

C t sec on of the l er h m ta a c carc noma (P mary les on n he rec un) The pa ent had ma ked ja nd ce due to complete l r on of the l epat c l s by tl e me asta c nod es at the h lum Ord nar ly jaund ce s abse t or f p e ent is ratl er m l l netasta c nal gna cy of the l er ho ve er t s ob er ed w th grea er frequency in secondary neoplasm than n the pr mary carc no na of th s organ

OXFORD MEDICAL PUBLICATIONS

Jaundice

ITS PATHOGENESIS AND DIFFERENTIAL DIAGNOSIS

ELI RODIN MOVITT, M D

ACTING CHIEF OF MEDICINE VETERANS ADMINISTRATION HOSPITAL OAKLAND CALIFORNIA DIPLOMATE OF THE AMERICAN BOARD OF INTERNAL MEDICINE MAJOR MEDICAL CORPS ARMY OF THE UNITED STATES (INACTIVE)



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AFFECTIONATELY
TO MY WIFE,
JENNIE

FOREWORD

ONE of the fairly common and often serious problems of practice is what to do with a patient with jaundice Shall one diagnose a stone in the common duct and ask a surgeon to operate, or shall one say that operation would be useless or perhaps even a method of terminating the patient s life? Often the decision must be made quickly because the longer one waits the more injury is wrought to the liver.

Although there is as yet no laboratory test or series of tests that will surely and in every case give the answer to this problem, there are tests that, when wisely interpreted, are very helpful In the last twenty years a new field of diagnostic art has been built up around them and much constructive work is still being done by the men who are making a special study of the problem In the last few years greater interest has been focused on this field because of the epidemic of infectious hepatitis that has plagued the armed forces Unfortunately much of the new knowledge has not yet been fully assimilated by the average internist or even by the average gastro-enterologist, and as a result many persons with serious hepatitis are being operated on futilely and worse than futilely Many a surgeon who now operates, hoping to find a stone in the common duct, would not do so if he had only had the patient properly studied beforehand by means of modern tests

Dr Movitt has gone deeply into this subject He has gathered into one place a large amount of helpful information, and with it all he has written with clarity and charm He holds the reader's interest on every page This is a book that every gastro-enterologist and internist would do well to keep within easy reach until he has had time to digest it.

WALTER C ALVAREZ, M D.

The Mayo Clinic
Rochester, Minnesota

PREFACE

Jaundice is as old as medicine It was one of the first signs of disease recognized by the physicians of antiquity Its appearance is so striking and so readily amenable to detection by even an inexperienced eye that it is not at all surprising to find that it was early recognized as an indicator of disease Galen gave a comprehensive description of clinical icterus

Jaundice does not constitute a pathological entity in itself but merely denotes an underlying pathological process whatever its nature and causation It is a sign common to many different morbid states and thus encompasses a wide field of clinical medicine In any individual case the determination of the nature and etiology of the disease process may be very difficult Upon review of clinical records one is impressed with the frequent lack of diagnosis of the causes of jaundice in patients referred to the hospital It is the purpose of this book to aid the practicing physician in the task of making the differential diagnosis in this important group of diseases The pandemic of infectious hepatitis in World War II gave renewed impetus to the interest in the general subject of jaundice and the present appearance of this small volume may therefore be considered timely

A proper orientation with regard to the subject under discussion is almost impossible without a clear understanding of fundamental concepts of related anatomical structures and pathologic physiology A great part of the first section in this book is devoted to the consideration of these topics In the discussion of numerous laboratory tests emphasis is laid upon the interpretation of results For the detailed description of the technics involved in these tests the reader is referred to many excellent texts of clinical laboratory procedures An attempt has been made to render the presentation of the subject as practical as possible

I am grateful to Dr Walter Alvarez for his helpful review of the manuscript I also wish to acknowledge the efficient assistance and courtesy of the staff of Oxford University Press New York

E R M

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PART I

'In the treatment of jaundice the first point to be considered is the causes which have led to the accumulation of bilious matter in the blood'

—FRIEDRICH THEODOR FRERICHS (1879)

CHAPTER I

THE ANATOMY OF THE LIVER AND THE BILIARY TRACT

Embryology

The liver first appears in human embryos as a diverticulum of the ventral wall of the fore gut near its junction with the yolk sac It projects into a mass of mesoderm a part of which is destined to form the diaphragm Solid cellular cords proliferate from the blind end of the hepatic diverticulum They extend upward on both sides of the gut and anastomose with each other to produce a meshwork of cell cords these will constitute the glandular portion of the liver The original hollow diverticulum is destined to become the biliary system of ducts with the gall bladder As the cords of the glandular organ expand they grow between the venous plexuses of the vitelline veins while the plexuses in turn make their way among and around the liver cords As a result a labyrinth of sinusoidal vessels envelops closely the periphery of the hepatic trabeculae The part of the vein below the liver is modified to form the portal vein which brings blood to the sinusoids The upper part which drains the blood from the sinusoids after its passage through the liver is the *hepatic vein*

The right and left lobes of the liver become recognizable first The caudate and quadrate lobes make their appearance later

Although the clear demarcation of individual liver lobules is not apparent until early childhood the process of lobule formation begins relatively early in the foetus The following description is from *Arey's Developmental Anatomy*

> The lobules or vascular units of the liver are created by the peculiar and regular manner in which the veins of the liver branch A primary division of the hepatic vein drains blood from the center of each primi

tive lobule and is parallel to similar branches of the portal veins that extend along the periphery of the lobule As development proceeds each central hepatic branch becomes a stem which both bifurcates at its tip and gives off side sprouts New lobules arise by the simple splitting of lobules which have thus acquired two central veins the plane of cleavage bisects the angle between forked vessels The portal vein likewise forms secondary branches which bear the same relation both to the new lobules and their central veins as did the primary portal branches to the first lobules This process is repeated during fetal life and early postnatal life until thousands of hepatic lobules are present

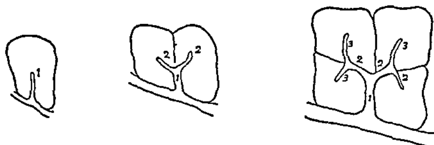


Fig 1 Diagram showing method of increase in number of lobules of liver From Johnson Courtesy of *Am J Anat*

According to a more recent view, the liver trabeculae described above are essentially tubular from the very start instead of being solid cords Thus tiny bile capillaries have their beginning They drain into larger interlobular ducts which may form from the trans formation of certain liver cords in response to the pressure stimulus of ingrowing connective tissue Through the intermediary of the still larger intrahepatic ducts a connection of the intralobular ducts is established with the hepatic duct that is continued in the common bile duct both representing the stem portions of the original hepatic diverticulum The gall bladder with its cystic duct represents a special offshoot of the same diverticulum in its early development

Gross Anatomy

The liver is the largest glandular organ in the body Its average weight is about 1500 grams It occupies the right upper part of the abdominal cavity It extends from the right hypochondriac region across the epigastrium to the left hypochondrium and also down

ward into the right lumbar region It is situated immediately be neath the diaphragm The greatest part of its lateral surface lies under the rib cage Only a comparatively small part of its anterior surface is in contact with the anterior abdominal wall Of the two main lobes of the liver right and left the right is the larger On the posterior surface of the organ two additional smaller lobes can be distinguished the caudate lobe toward the superior border of the liver and the quadrate lobe toward the inferior border

The bile elaborated by the liver cells is collected by microscopic intercellular capillaries which join collectively to form the intra lobular canaliculi and as such drain into interlobular bile ducts By confluence and usually outside the liver tissue the latter eventually form the two main branches which unite to give rise to the hepatic duct The right branch is formed by union of the interlobular ducts of the right and quadrate lobes of the liver while the left branch takes its origin from the interlobular ducts of the left and caudate lobes The hepatic duct along with the distal portions of its two contributaries constitutes the origin of the extrahepatic biliary passages while the other channels above described are known under the collective name of the intrahepatic duct system More will be said about the latter in the discussion of the microscopic structure of the liver

The gall bladder is a conical or pear shaped fibro muscular organ that is situated in a fossa on the under surface of the liver the fossa separates the right lobe from the quadrate lobe The normal gall bladder has a capacity of 30 to 50 cc At the tapering end or neck it is continued through the ampulla into the cystic duct which unites with the hepatic duct to form the common bile duct or ductus choledochus The junction between the two occurs at various angles The ductus choledochus is about 7 to 9 cm long It passes behind the superior portion of the duodenum and then in a groove near the right border of the posterior surface of the head of the pancreas (an important relationship) Occasionally it may be completely im bedded in the pancreatic substance The pancreatic part of the duct then passes downward and terminates by penetrating the posterio mesial side of the descending duodenum at about its middle The intraduodenal portion of the common duct enters the gut obliquely and is joined by the pancreatic duct The junction of the two ducts gives rise to the ampulla of Vater which is about 2 mm in length

and which becomes constricted and opens into the duodenum on the summit of the duodenal papilla This opening is quite small The ductus choledochus itself may also be narrowed before entering into the ampulla of Vater There is no unanimity of opinion upon the mode of termination of the bile and pancreatic ducts While some investigators find that there is an ampulla common to both ducts in the majority of individuals others consider this to be an unusual arrangement finding that the two ducts open separately into the duodenum each on the summit of a small papilla

An important anatomical structure at the terminal portion of the common bile duct is the sphincter of Oddi It consists of several sets of smooth muscle surrounding the intraduodenal portion of the bile duct (or ducts in the case of union of biliary and pancreatic passages) and extends from a level just outside the choledochal fenestra in the duodenal wall to a level near the lower end of the ampulla of Vater The hepatic duct and the ductus choledochus down to the ampulla possess little muscle elements simply representing fibro elastic tubes with very little muscle The opening of the ampulla is so small that gallstones having passed the cystic and the common ducts often become impacted Pancreatic as well as bile secretions may then be prevented from entering the duodenum unless a communication exists between the main and accessory pancreatic ducts This favors reflux of bile into the pancreas with consequent pancreatitis The common bile duct sometimes narrows a little before opening into the ampulla of Vater and causes impaction of stones

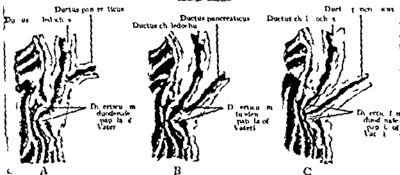
The biliary duct system is universally known for the frequency with which anomalies in anatomical relationships are known to occur For example the two hepatic ducts may empty directly into the gall bladder In such cases the common duct starts from the neck of the gall bladder and the cystic duct is absent Accessory hepatic ducts opening directly into the gall bladder are also known

Histology

The basic structural unit of the liver is represented by the liver lobule Just as a brick wall is composed of individual bricks held together by a cementing substance the liver is composed of a great number of minute individual lobules held together by the con

Collum vesicae felleae
Valvula spiralis (Heisteri)
Vesica fellea
Ductus cysticus
Ductus hepaticus
Pars superior duodeni
Tunica mucosa vesicae felleae
Plicae tunicae mucosae
Diverticulum duodenale
Ductus choledochus
Ductus pancreaticus
Pars descendens duodeni
Pars horizontalis duodeni
Flexura duodeni inferior

FIG. 2 Gall bladder and bile ducts and their relations with the duodenum From C. L. Callander *Surgical Anatomy* Courtesy of W. B. Saunders Co



necting tissue of the periportal spaces with their network of blood vessels nerves and lymphatics All the functions of the liver represent the sum total of physiological processes taking place in these individual parts The liver lobule thus bears the *same* relation to the *whole organ* as the nephron does to the kidney Each liver lobule contains all the elements of the liver Every lobule may be regarded as an elementary liver and the entire organ a collection of miniature livers

Three basic structures enter into the formation of a lobule They are parenchymal liver cells bile canaliculi and blood vessels Their orderly interrelation must be understood in order to grasp the picture of the unit in its entireness The lobule may be conceived of both in terms of a vascular and parenchymal organization

The liver lobule is usually described as a polygonal prism that in cross section has from five to seven sides the diameter of the cross section being smaller than the height of the lobule The outlines of the lobules are usually not distinct because the connective tissue partitions between them are poorly developed These partitions take their origin from the condensed connective tissue at the porta (hilum) of the liver where it envelops the portal vein hepatic artery hepatic ducts lymph nodes lymphatic vessels and nerves The connective tissue known as the capsule of Glisson continues into the liver to form a sheath about these structures and separates them from the liver parenchyma The extensions of the capsule into the organ are known as periportal spaces they carry with them the blood vessels such as branches of the portal vein (interlobular veins) that convey blood to the liver from the digestive tract and the branches of the hepatic artery as well as the interlobular bile ducts and lymphatics

The liver cells are arranged within each lobule in cords that radiate like the spokes of a wheel from the center which contains a central vein leading toward the periphery Toward the central vein converge the capilliform sinusoids coursing in between the hepatic trabeculae All the central veins empty into sublobular veins These come together to form the main branches of the hepatic vein which carries away from the liver the blood brought to it both by the portal circulation and the hepatic artery Thus the flow of blood is from the portal veins (in the periportal spaces or portal canals) through the capilliform sinusoids to the central veins.

thence through the sublobular veins into the hepatic vein which empties into the inferior vena cava The question whether or not there are communications between branches of the hepatic artery and portal vein radicles within the interlobular spaces before the vessels enter the liver lobule remains unanswered It is believed by some that the unmixed arterial blood passes directly into the liver sinusoids through small branches of the hepatic artery If it is true that the arteries empty through capillaries directly into the sinusoids

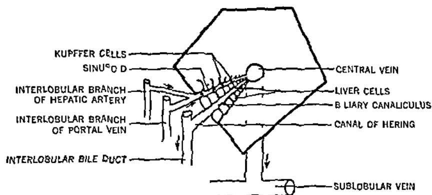


FIG 4 Diagram of a liver lobule

adjacent to the portal canals the hepatic cells at the periphery of the lobule are better nourished than those toward the center

The liver cell cords are separated from one another by the sinusoids These are irregular and tortuous blood spaces that pursue in general a radial course in the lobule As explained above they connect the small branches of the interlobular portal veins with the intralobular central veins in addition to receiving some blood from the branches of the hepatic artery

The sinuses are lined by two types of cells The protoplasm of one of these extends as a thin film along the sinusoid forming its wall so to speak The other type is the stellate or Kupffer cell known for a long time to be highly phagocytic The cells of the latter type do not seem to be lining the sinusoids but are actually anchored in the blood stream While the undifferentiated lining cells fail to take up vital dyes the Kupffer cells store large amounts in granular form and are the[illegible] classified as belonging to the system of histiocytes or mac

While on one side the liver-cell trabeculae are separated from each other by venous sinusoids on the other side there are found coursing between them the bile canaliculi into which the constituents of the bile are emptied by the hepatic cells These cells thus have a dual anatomic relationship being in intimate contact with the biliary radicals and with the vascular channels carrying the blood to and away from the liver About the liver cells and in close relation to the vascular capillaries there are in addition lymph spaces (the spaces of Disse)

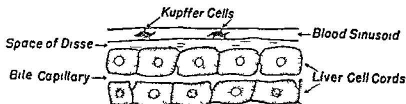


Fig 5 Disse s spaces in relation to the blood s nuso ds and the cords of the liver cells

The bile canaliculi have intercellular branches that end blindly and that do not completely separate adjoining cells of the liver cords because they never quite reach the blood sinusoids The bile canaliculi connect with the interlobular ducts in the periportal spaces by means of canals of Hering These connecting pieces between the bile capillaries which are lined by the liver cells and the larger ducts in the periportal fields are represented by short channels having a wide lumen and a weak wall both lined by flat epithelium

BIBLIOGRAPHY

Arey L B *Developmental Anatomy* Philadelphia W B Saunders 3rd ed Revised 1934
Callander C L *Surgical Anatomy* Philadelphia W B Saunders 1939
Cameron A L and Noble J F *J A M A* 82 1410 1924
Gray H *The Anatomy of the Human Body* Philadelphia Lea & Febiger 12th ed 1918
Hendrickson W F *Bull Johns Hopkins Hosp* 9 221 1898
Job T T *Anat Rec* 32 212 1926
Lewis F T and Bremer J L *A Text Book of Histology* Philadelphia P Blakiston s Son & Co 2nd ed Revised 1927
Mann F C and Giordano A S *Arch Surg* 6 1 1923
Maximow A A *A Text Book of Histology* Philadelphia W B Saunders 1930

Oddi R *Arch ital de biol* 8 317 1887
Olds J J and Stafford E S *Bull Johns Hopkins Hosp* 47 176 1930
Opie E L *J A M A*, 43 1102 1904
Smith J V Personal Communication
Walton J *Surg, Gynec and Obst*, 79 56 1944

THE PHYSIOLOGY OF THE LIVER

The excretion of bile is the most obvious function of the liver. However, long before the knowledge of the physiology of the liver had reached its present status astute students of the subject had suspected that nature would hardly have made the organ so large for the sole purpose of producing bile, a secretion whose amount is not greater than that of urine. The weight of the liver is several times that of the combined weight of both kidneys (1500 gm as against 280 or 300 gm)

The liver has many functions intimately associated with other physiological activities of the body. These manifold functions are principally concerned with secretion of bile, metabolism, storage, detoxification, and the mechanism of blood coagulation. They are listed below in outline form

Hepatic Functions

I Secretory Function (Chologenesis)
 Formation and secretion of bile
II Metabolic Functions
 1 Carbohydrate metabolism
 2 Protein metabolism, deamination, amino acid, urea and uric acid synthesis
 3 Fat metabolism
 4 Mineral metabolism and regulation of acid base equilibrium
 5 Water metabolism
 6 Heat production
 7 Vitamin production
III Storage Function
 1 Vitamin storage
 2 Iron and copper storage
 3 Storage of hematopoetic principle
IV Detoxification

V Scavenger Function
Reticulo endothelial activity (Kupffer cells)
VI Blood Coagulation
1 Production of fibrinogen
2 Production of prothrombin
3 Blood platelets
VII *Blood Formation (in the embryo)*
VIII Regulation of Blood Volume
IX Function of Regeneration

The major functions of the liver are (1) to secrete bile, essential for proper utilization of certain foodstuffs, (2) to supply a constant stream of foodstuffs to the different tissues of the body for quick transformation into energy, and (3) to regulate the blood-clotting mechanism The first function is to a certain degree replaceable by substitution therapy (with bile salts) The second cannot be taken over by any other organ in the body or by any extraneous agent or means, so that life itself ceases with the cessation of the work of the liver

The multiplicity of activities of the liver is amazing Its metabolic functions are of prime importance in the economy of a living organism The liver, which has been referred to as the commissariat of the body, is a storehouse of utilizable food for the organism as a whole In the words of Mann

The liver is a large storage and manufacturing plant, constantly teeming with activity Through its vast sinusoids which are in intimate relationship with the multitude of hepatic cellular units, are transported the various materials upon which the tissues of the body must rely for their source of energy, growth and repair and for the necessities for maintaining the processes of life Some of these substances are capable of being used directly by the tissue cells and the liver only stores them during periods of plethora Other substances are more crude and the liver transforms them into a utilizable form One must imagine that within the hepatic cells are tools probably enzymes, for making possible the storage and manufacture of these essential substances Coming to the hepatic cells must be numerous chemical messengers to correlate hepatic activity to the varying needs of the body Finally it should be noted that this vital stream to and from the liver must persist, even during dearth of material bodily disease and hepatic impairment as long as life exists

The liver removes from the circulation the food materials absorbed from the gastro intestinal tract during the plethora associated with digestion By means of storage synthesis and regulatory activities it is capable of adopting the various amounts of food that enter the organism to the changing requirements for such materials to the tissues Thus hepatic activity is responsible for the regulation of the more important supplies of food At least the function of maintaining the glucose concentration in the blood is vital to the extent that its loss is shortly followed by death

Secretion of Bile (Chologenesis)

This function of the liver is closely related to the intrahepatic circulation as the principal constituents of the bile are derived from certain elements carried to the liver by the blood stream It will be recalled from the discussion on the anatomy of the liver that this organ has a double blood supply The relative amounts of blood that reach the liver through either the arterial or venous component vary Usually the hepatic artery contributes only from an eighth to a fourth of the total blood flow through the liver Thus the hepatic blood supply is unique in that the greater part of the blood flowing into it is venous There is a reciprocal response between the flows in the hepatic artery and the portal vein—if flow increases in one it decreases in the other The liver has great functional reserve in the activity of the vascular system and under ordinary conditions only about a fourth of the hepatic circulation is active

Increase in portal blood flow augments the volume output of bile Chologenesis is not arrested completely but only diminished after sudden complete exclusion of the portal vein the liver apparently being capable of secreting bile as long as its arterial supply is intact Neither does hepatic artery occlusion prevent formation of bile as long as the portal circulation is intact

Normally bile is secreted continuously by the liver cells but the rate of flow and concentration of different constituents vary depending on many factors The kind of food ingested influences variations in volume and character of bile Under certain conditions a complete suppression of the biliary secretion (complete acholia)

may take place A functional disturbance of the organ, as well as obstruction in the biliary passages may lead to suppression of bile After complete occlusion of the biliary tract the liver may continue to secrete for a while, but after the pressure in the distended ducts reaches a certain critical level, this particular product of hepatic cells is turned back into the organism In a dog bile ceases to be secreted when the pressure in the ducts reaches 350 mm, as this exceeds the secretory pressure of the liver Also the quality of the secretion may change under continually elevated pressure The daily biliary output in man has been estimated to amount to about 500 cc

Nervous regulation of bile flow probably also exists Thus stimulation of the splanchnic or hepatic nerves has been found to decrease, and their severance to increase the amount of bile produced by the liver

The bile secreted by the hepatic cells into the bile canaliculi passes along the interlobular ducts into the hepatic duct and then into the gall bladder through the cystic duct. It is stored in the gall bladder, from which it is expelled through the ductus choledochus into the duodenum This expulsion of bile into the digestive tract takes place intermittently, in relation to the time of arrival of food in the intestine and independently of the actual secretion by the liver

Filling of the gall bladder takes place during the initial stages of digestion Foods in the gastro intestinal tract and the hormones elaborated by the intestinal mucosa cause the gall bladder to contract by a chemical mechanism Also nervous influences probably play some role The pressure in the ducts gradually rises as the digestion progresses, and when it reaches a certain critical point the sphincter of Oddi relaxes and the bile is discharged from the ducts into the duodenum Some of the bile secreted by the liver is discharged directly into the duodenum In the gall bladder the bile undergoes concentration

The bile secreted by the liver cells is a very complex fluid The physiological significance of all its constituents is not known The chief

The

of glycocholic and taurocholic acids It is not known [illegible] whether these salts are formed by the liver cells or are merely

brought preformed to the liver by the blood The evidence presented for formation of bile salts by the liver is quite convincing and in hepatic damage the amount of bile salts found and excreted may be greatly reduced The bile acids are so vital to the organism that only in extreme cases of liver damage (acute yellow atrophy) is there a decrease in bile acids in the blood and urine The dietary factors may influence the amount of bile salts formed and after their passage with the bile into the intestine they are reabsorbed and carried in the portal blood stream back to the liver for re excretion It is thought that the bile salts absorption and elimination in the bile is quantitative If this is true however a living organism would soon turn into a pillar of bile salts unless it possessed some mechanism for eliminating or destroying them It is possible that the liver is also concerned with the destruction of bile salts

The biliary pigment is derived from hemoglobin of disintegrated red blood cells More will be said later about the metabolism excretion in the bile and reabsorption from the intestinal tract of this clinically important constituent of the bile

The cholesterol is also abstracted by the liver from the blood stream A biliary portal circulation of cholesterol is known to be similar to that of the other bile constituents above mentioned What useful purpose may be served by cholesterol in the bile is not known and for the present it is of more pathological than physiological significance

Bile on entering the intestinal tract plays a very important role in the digestive processes It increases considerably the fat splitting power of pancreatic lipase dissolves fatty acids enhances the action of trypsin on proteins and makes possible the absorption of vitamin K from the intestines into the circulation Bile salts aid in the absorption of all fat soluble vitamins Some deleterious effects of lack of bile result from the loss of this function

METABOLIC FUNCTIONS OF THE LIVER

an

All metabolic functions of the liver are mediated by enzdual systems through which the different components of food are s differ processed In liver damage the dysfunction of these enzymenown to can well be expected To understand fully deviations with syn normal in the metabolic processes of the liver as there with re

generation of serum albumin which leads to hypoproteinemia with disturbance in the normal albumin/globulin ratio in the blood Hypoproteinemia is thus a rather constant finding in hepatic damage and frequently cannot be corrected by high protein diet as long as liver insufficiency continues to exist

Deaminization of amino acids also takes place in the liver The liver *in addition synthesizes urea from amino acids* The process of urea formation from ammonia has great biological significance since the latter is many times more toxic than the former After total extirpation of the liver the amino acid concentration in the blood rises With removal of the liver the normal processes of amino acid utilization cannot proceed in an orderly fashion While the results of animal experimentation are unequivocal in this regard clinically in patients with liver damage the evidence is inconclusive The amino acid concentration in the blood may not rise appreciably except in the terminal stages of liver poisoning Apparently because of tremendous reserve liver damage must be extreme to affect amino acid metabolism However in instances of severe hepatic injury two amino-acids tyrosine and leucine may assume a prominence and be recovered in significant amounts in the urine Presumably the increase in blood concentration of these two substances is attributable to general failure at deaminization but it is also possible that they may be derived at least partly from the autolysis of the liver cells overwhelmed by a toxemic process

While part of amino acids absorbed from the digestive tract are re synthesized into protein of the living tissue or utilized for production of specific secretions some are used for fuel In the decomposition of the amino acids used for fuel 58 per cent of the protein molecule is converted into glucose by the liver The intermediary metabolism of the amino acids which raise the metabolic rate and thus are responsible for the specific dynamic action of the proteins probably also takes place in the liver

Fat Metabolism

Although the liver cannot be regarded as a true depot place or storehouse of fat some fat is known to be stored in it The content of fat in this organ varies markedly and may be increased appreciably under pathological conditions (liver poisoning infectious processes in general starvation) The liver plays an important role

in intermediary fat metabolism It primarily desaturates fat to make it available for use as a fuel or for formation of essential parts of living tissue (cell membrane)

The deposition of fat in the liver is influenced by certain factors Choline derived from lipids (lecithin) and now known to be an essential dietary constituent exerts an important effect on the transport and storage of fat Thus the production of fatty livers in dogs by removal of the pancreas can be prevented by administration of lecithin The active component of lecithin was identified as choline Betaine casein and methionine (a constituent of casein) have a similar lipotropic effect on the mobilization of fat Whenever these lipotropic factors are lacking in the diet the liver content of fat rises appreciably Fat deposition in the liver is influenced also by pituitary activity and insulin The administration of insulin prevents the deposition of fat in the liver of the diabetic animal and promotes instead the deposition of glycogen Generally speaking the glycogen and fat content varies in an inverse ratio Thus in fatty livers the stores of glycogen are at a low ebb while in those of healthy individuals in a good state of nutrition glycogen abounds and fat content is low However moderate amounts of glycogen can accumulate in moderately fatty livers

It is now definitely known that the ketone bodies which are the products of intermediary metabolism of fats are produced in the liver Thus ketonuria responsible for acidosis in a patient with uncontrolled diabetes mellitus is the result of overproduction of ketone bodies by the liver and represents the attempt to meet the metabolic needs of the organism which is unable to utilize carbohydrates in the presence of insulin deficiency Ketone bodies take the place of carbohydrates to provide the necessary source of energy liberated by the tissues in the process of their oxidation to carbon dioxide and water A great proportion of the total energy requirements of the organism may be provided in this manner Ketone bodies are formed not only when there is failure of carbohydrate oxidation i e inability to utilize carbohydrate properly (diabetes) but also in conditions characterized by a low glycogen content of the liver i e when the organism is able to oxidize sugar but is lacking in it (starvation)

Of the fats in the metabolism of which the liver plays a significant role cholesterol may be singled out here for the purpose of

discussing certain specific features of its metabolism Cholesterol is an essential constituent of living tissues and fluids It is known to exist in the free state and also combined with the fatty acids as esters Its concentration in the bile varies with the amount of it in the blood Whereas in the bile it occurs only in the free state in the blood more than half is present as the ester (50 to 75 per cent) *It is important to know that esterification of cholesterol takes place in the liver* Tissues other than liver may be capable of cholesterol synthesis In severe liver damage the total blood cholesterol is diminished and the ester fraction may almost completely disappear

Other Metabolic Activities of the Liver

The liver has a part in regulation of the ionic equilibrium of the body

Iron an indispensable constituent of hemoglobin is stored in the liver as well as in the spleen and kidneys Its content in the liver is about 0 05 per cent Copper which may act as a catalyst in hemoglobin synthesis is also stored there

It is believed although some of these assumptions are more or less hypothetical that the liver plays a rôle in water metabolism having something to do with the regulation of the water balance This influence may be mediated to some extent by hormonal factors The problem is related to the regulation of circulating blood volume in which the liver may be acting as a blood depot The storage of blood in the organ or its release into general circulation may be mediated in man by a variety of different mechanisms such as the activity and inactivity phases of the hepatic sinusoids and capillaries and by lymphatic drainage

By virtue of numerous chemical reactions carried on in the liver as a part of general metabolism this organ serves (along with the muscular tissue) as one of the main sources of the body heat

The liver serves as the site of formation of vitamin A from carotene It also stores *this vitamin along with others* More will be said about vitamin storage *in the next section*

Among other essential substances manufactured by the liver are prothrombin and fibrinogen which are indispensable in the mechanism of blood coagulation This important phase of liver *function* will be discussed in greater detail under blood clotting

Storage Activities of the Liver

That the liver stores vitamins A and D has been known for a long time and fish liver oils have for many years been used as a source of these two vitamins for medicinal purposes

Although the knowledge of the role of the liver in the metabolism of vitamin B is incomplete compared with that of vitamin A there is no doubt that an important interrelationship exists The vitamin B fractions are apparently stored in the liver and the liver may also have some influence on utilization of this principle by the organism For example in the presence of hepatic damage (alcoholic cirrhosis) the associated peripheral neuritis may fail to respond to administration of thiamine In fact cirrhosis itself may be etiologically related to vitamin B deficiency

The liver serves as the largest depot of vitamin C in the body and also stores vitamin K which is indispensable for prothrombin formation in that organ

In hepatic disease the stores of all vitamins mentioned above may be severely depleted leading to development of symptoms and signs of avitaminosis

The anti anemic principle needed for orderly hematopoiesis and formed in the digestive tract through interaction of the extrinsic factor in the food and the intrinsic factor provided by gastric secretions is also stored in the liver and may be depleted in intra hepatic disease

Detoxification and Scavenger Activity of the Liver
(*Reticulo Endothelial Activity*)

By means of conjugation with certain amino-acids (cystine glycine) glycuronic acid (oxidation derivative of glucose) and sulphuric acid the exogenous poisons entering the circulation from the gastro intestinal tract are rendered harmless in the liver It is well known that indole skatole and phenol formed by bacterial action on fecal matter and absorbed into the circulation are conjugated with glycuronic or sulphuric acids Conjugated glycuronic acids are more easily excreted in the urine In fact it may be incorrect to refer to the above mentioned conjugating reactions as detoxifying proc

esses thus ascribing a teleological significance to certain properties of liver function which may actually have for their purpose mainly the object of rendering substances more acid and more easily excretable by the kidneys For example benzoic acid is conjugated in the liver with glycine to form hippuric acid which is excreted in the urine But benzoic acid is nontoxic Its conversion into hippuric acid merely makes it more readily excretable Probably both the liver parenchyma proper and the reticulo endothelial system (Kupffer cells) along with the hepatic capillaries are responsible for so called detoxification The liver is also capable of abstracting from *the circulation certain substances foreign to normal metabolism* and of fixing them within itself It may be mentioned in passing that certain substances not foreign to normal metabolism but rather representing different indispensable substances or hormones also can be inactivated by the liver (estrogens) The metabolism of estrogenic hormones is deranged in liver damage Insoluble particles foreign colloids and bacteria are removed from the blood stream by the Kupffer cells

Blood Formation

While in the later part of prenatal life the bone marrow assumes the role of a blood forming organ it is the liver that performs this function in the earlier stages of fetal development In the adult the liver may revert to the prenatal state of a blood forming organ when the orderly process of hematopoiesis in the bone marrow is interfered with by disease involving the marrow (myeloid metaplasia)

Blood Coagulation

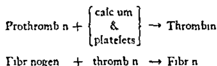
The liver plays an important part in regulating the clotting *properties of blood Coagulation involves two consecutive reactions* the first step is the formation of an active coagulant thrombin the second step consists of the interaction between thrombin and fibrinogen to form fibrin

Thrombin is formed from a plasma factor that serves as its precursor and is known as prothrombin The conversion of prothrombin into thrombin depends upon *the interaction of two substances* (1) Thromboplastin a substance derived from blood platelets and also present in tissue extracts In plasma free of platelets it may be

present in traces However clotting of plasma freed from platelets is very slow or altogether absent (2) Calcium ion

Many theories of blood clotting have been proposed since the original one promulgated by Alexander Schmidt in 1861 The theory proposed by Eagle is the least complicated and explains the process on the basis of two consecutive enzyme reactions The blood platelets act in conjunction with calcium to form an enzyme which activates the thrombin precursor prothrombin transforming it into thrombin Thrombin acts as an enzyme to activate fibrinogen to produce fibrin

TABLE I



It is clear from a glance at Table I that the deficiency of either prothrombin fibrinogen calcium or platelets may lead to defective clotting The liver has something to do with the formation of two of these factors (fibrinogen and prothrombin) and possibly with the regulation of the last mentioned element (blood platelets) The liver as the site of formation of fibrinogen and prothrombin has already been mentioned Its role in the production of prothrombin will now be discussed in greater detail That the liver participates in the mechanism of blood clotting has been suspected for a long time The hemorrhagic tendency and decreased coagulability of blood in patients with jaundice had been recognized long before the nature of this participation was elucidated

Now it is a well established fact that the liver is at least the chief source of prothrombin Thus in liver damage hypoprothrombinemia may supervene leading to prolongation of coagulation time and manifestation of hemorrhagic tendency The removal of the liver in animals causes a prompt decrease in the concentration of prothrombin in the circulating blood while with partial hepatectomy the prothrombin decrease is in some measure correlated with the amount of liver removed Whenever the prothrombin concentration in the blood falls to about 30 to 20 per cent of normal bleeding tendency may manifest itself It is also known that vitamin K

governs the formation of prothrombin This fat soluble vitamin cannot be absorbed from the digestive tract in the absence of bile salts Thus the liver serves a threefold purpose it not only manufactures prothrombin and stores it but is also essential for absorption from the intestine of the vitamin K necessary for prothrombin formation In obstructive jaundice even in the initial stages when the liver parenchyma is not as yet profoundly effected there will result a deficiency in prothrombin because of the exclusion of bile with its salts from the digestive tract In such instances the injection of vitamin K intravenously produces a prompt restoration of the normal blood coagulation mechanism

From this discussion it will be clear that hypoprothrombinemia may result from diverse conditions which either cause interference with production of prothrombin in the liver in the presence of vitamin K (liver damage) or interfere with delivery of vitamin K to the liver from the digestive tract because of absence of the bile salts in the intestine (as in obstructive jaundice or complete external biliary fistula) or even in the presence of bile salts because of malabsorption from the digestive tract due to disease of the bowel (sprue ulcerative colitis) As fibrinogen another essential link in the process of blood coagulation is also formed in the liver fibrinopenia with bleeding tendency could be expected to exist in cases of liver damage Evidence to the effect that such a situation may actually arise has been presented

It will be recalled that blood platelets are necessary for blood clotting Thrombocytopenia is frequently found in liver disease and may thus serve as a contributory factor in the derangement of clotting mechanism and hemorrhagic diathesis However a definite and consistent correlation between blood platelet count and liver damage on the one hand and hemorrhagic tendency on the other is lacking It is not known by what mechanism the liver function

anti anemic principle which governs orderly maturation of erythroblastic elements in the bone marrow the liver may also produce or store some as yet unknown factor that influences the development in the bone marrow of megakaryocytes from which the platelets are derived

Function of Regeneration and Reserve

The reserve capacity of the liver is remarkable A great part of the organ may be rendered useless by disease process and still the remaining often surprisingly small amount of the functioning liver tissue left may be sufficient to carry on business as usual It requires less than 20 per cent of the normal bulk of the organ to maintain its function No less remarkable is the ability of liver tissue to re generate As much as three quarters of the organ may be removed leaving the animal not only surviving but also regenerating prac tically the entire organ After liver damage subsides or as it is sub siding the old lobules sprout to give rise to new ones which estab lish connections with the newly formed biliary channels

BIBLIOGRAPHY

Addis T Poo L J and Lew W *J Biol Chem*, 115 111 1936

Andrus W de W Lord J W and Moore R A *Surgery* 6 899 1939

Auster L S and Crohn B B *Am J Med Sci* 164 345 1922

Best C H Hershey J M and Huntsman M E *J Physiol* 86 190 1932

Best C H and Taylor N B *The Physiological Basis of Medical Practice* Baltimore The Williams & Wilkins Co 3rd ed 1943

Bollman J L Mann F C and Magath T B *Am J Physiol*, 69 371 1924 ibid 78 259 1926

Cameron G R and Mayes B T *J Path and Bact* 33 799 1930

Eagle H *Medicine* 16 95 1937

Elman R and Heifetz C J *J Exper Med* 73 417 1941

Ham T H and Curtis F C *Medicine* 17 413 1938

Hershey J M and Soskin S *Am J Physiol* 98 74 1931

Leary T *Arch Path* 32 507 1941

Leathes J B and Raper H S *The Fats* New York Longmans Green & Co 1925

Lichtman S S *Diseases of the Liver Gallbladder and Bile Ducts* Philadelphia Lea & Febiger 1942

Lusk J M *J Biol Chem* 115 491 1936

Machella T E and Higgins G M *Proc Staff Meet Mayo Clinic* 16 174 1941

Mann F C *Am J Digest Dis and Nutrit* 4 355 1937

Mann F C and Bollman J L *Arch Path and Lab Med* 1 681 1926 *Ann Int Med* 9 617 1935

Mann F C and Magath T B *Arch Int Med* 30 73 1922

Smith H P Warner E S and Brinkhous K M *J Exper Med* 66 801 1937

Soskin S Allweis M S and Cohn S J *Am J Physio*, 109 155 1934

Stadie W C Zapp *J A* and *Lukens F S W* *J Biol Chem* 137 75 1941
Symposium on Respiratory Enzymes Madison Univ of Wisconsin Press 1942
Tanturi C A and Ivy A C *Am J Physiol* 121 61 1930
Taub S J Shlaes W H and Rice L *Ann Int Med* 22 852 1945
Warren R. and Rhoads J E *Am J Med Sci* 198 193 1939
Whipple G H and Smith H P *J Biol Chem* 80 685 1928 ibid 89 727 1930
Wintrobe M M *Clinical Hematology* Philadelphia Lea & Febiger 1944

CHAPTER III

THE METABOLISM OF THE BILE PIGMENT

As the bile pigment is responsible for the yellow discoloration of the skin in this condition a knowledge of bile pigment metabolism is essential for the understanding of different problems presented by clinical jaundice Normally the pigment is excreted as a waste product and is not known to perform any useful function in the body economy However its origin and mechanism of formation have physiological significance while its clinical significance resides in its role as a visible indicator of disease

The biliary pigments are bilirubin the chief pigment in human bile and biliverdin derived from the former by oxidation and present in human bile only in small amounts (it is the chief pigment in birds bile)

Bilirubin is derived from hemoglobin and is the porphyrin fraction globin free and iron free of the hemoglobin molecule It will be recalled that hemoglobin is a conjugated protein consisting of an iron-containing pigment portion (porphyrin) combined with a protein called globin Porphyrins are widely distributed in nature For example chlorophyll—the green coloring matter of plants—has a porphyrin as its pigment base Porphyrins are capable of forming compounds with various metals protoporphyrin combined with iron forms the metallo-porphyrin of the blood pigment

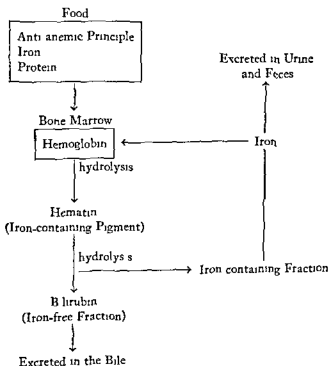
The life span of red blood cells is limited and as the senescent cells disintegrate their place is taken by the newly formed ones Thus blood destruction goes on continuously and is indicated by the presence of small amounts of bilirubin in the blood stream (0 2-0 8 mg per 100 cc) This bilirubin is derived from the hemoglobin of broken-down red blood cells The breaking down of erythrocytes takes place in the reticulo endothelial system situated in various parts of the body such as spleen lymph nodes bone marrow and liver (Kupffer cells) In other words the liver is not solely

responsible for formation of bilirubin, and more important extra hepatic sites of pigment formation exist

Hemoglobin is probably first converted into globin and the iron containing pigment is freed of its iron and thus converted into bilirubin The liberated iron in its major portion is probabl stored in the liver, to be used again upon delivery to the bone marrow for erythrocyte formation Small amounts are excreted in the urine and feces The ultimate fate of globin is not definitely known but it may be converted into amino acids and used again in hemoglobin formation

TABLE II

IRON METABOLISM



Bilirubin is brought by the blood stream to the liver The parenchymal cells of the liver have a great power of absorbing it from the circulation and excreting it into the bile canaliculi along with the other constituents of the bile (There is some evidence that bilirubin along with everything else that enters the hepatic cells

first passes through the Kupffer cells) Thus the main function of the liver in relation to bilirubin is not to produce but to excrete the pigment The kidneys also excrete bilirubin to a small degree

The pigment excreted by hepatic cells into biliary canaliculi passes through the main bile ducts into the intestine Unchanged bilirubin probably is not reabsorbed from the digestive tract back into the circulation However in the intestinal tract it undergoes reduction by bacteria to form urobilinogen (also called sterco bilinogen) and in that form is partly reabsorbed into the blood stream A part is excreted in the stool and by oxidation is con verted to urobilin (stercobilin) in which form it is identified in a stool specimen by special laboratory procedures It may be noted in passing that urobilin has nothing to do with the coloring matter of the stool

Urobilinogen reabsorbed from the intestine into the circulation is brought by the portal stream to the liver which removes it from the blood almost completely and re excretes it into the bile Thus urobilinogen normally present in the bile merely represents a pig ment re excreted after its absorption from the intestinal tract When

TABLE III

METABOLISM OF THE BILE PIGMENT
The bile pigment bilirubin is derived from hemoglobin This conver sion takes place in the reticulo-endothelial system Bilirubin is then brought by the blood stream to the liver Thus the main function of the liver in relation to bilirubin is not to produce but to excrete the pigment Bilirubin is excreted by the hepatic cells into the biliary channels and is carried away with other constituents of the bile into the intestinal tract where it is converted into urobilinogen Part of urobilinogen is reabsorbed from the intestinal tract into the circulation which carries it to the liver for re excretion A small fraction of reabsorbed urobilinogen filters through the kidneys Urobilinogen excreted in the feces and urine is promptly con verted into urobilin In health most of the urobilin appears in the stool and only a very small quantity is recovered from the urine However in liver disease the hepatic cells may not be able to abstract efficiently from the circulation urobilinogen reabsorbed from the intestinal tract and as a result urobilinogen can be recovered from the urine in increased amounts In complete biliary obstruction urobilin disappears from both the feces and urine for obvious reasons as the bile cannot gain access to the digestive tract no bilirubin remains there for conversion into urobilinogen

the entire output of bile is collected through a complete fistula (none being allowed to enter the bowel) there is complete disappearance of urobilinogen from the bile after the pigment already

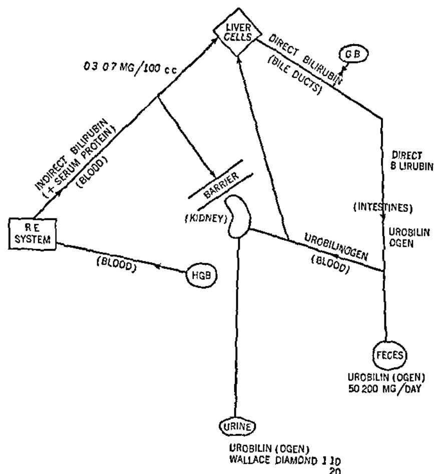


FIG 6 Diagrammatic representation of the normal bilirubin metabolism From W Dameshek and K Singer Courtesy of *Arch Int Med*

present in the intestine prior to the diversion of biliary stream has been carried away in the feces So nearly complete is this removal of reabsorbed urobilinogen from the blood by the normal liver, that very little of it remains in the circulation to reach the kidneys which are also capable of excreting it Thus, in a normal individual *only a very small amount of urobilinogen is recovered* in the urine However, in liver disease the function of the organ to remove re

CHAPTER IV

THE PATHOGENESIS OF JAUNDICE

Different Mechanisms of Jaundice Production

Bile pigment is responsible for the yellow color of the skin in jaundice It is worth remembering that in the absence of bilirubin in the skin icterus may be simulated by carotene and atabrine A diet of carrots may give to the skin and blood serum a peculiar yellow tinge known as carotinemia The sclerae however remain unaffected This condition is extremely rare is entirely harmless and disappears after removing the vegetable from the diet It is more important to bear in mind atabrine as a possible source of error for the number of people treated with this drug materially increased during World War II When pigmentation is attributable to carotene or atabrine the concentration of serum bilirubin is normal and the van den Bergh reaction is indirect The faint yellowish tinge of normal blood serum is probably due to minute traces of bilirubin usually present in health In jaundice the yellow color is visible in the conjunctivae before it can be detected in the skin and it varies in intensity from a light yellow to a deep dirty brown color All gradations from an orange tint to a greenish or bronze hue are encountered

In this chapter we are concerned with the mechanism or mechanisms responsible for excess accumulation of bile pigment in the blood and leading to its diffusion into various tissues of the body *including skin where its recognition establishes clinically the presence of jaundice*

Some phases of the knowledge of bile pigment metabolism discussed in the chapter on physiology will now be briefly summarized Bilirubin is formed from hemoglobin of the disintegrated erythrocytes This transformation takes place *in the reticulo-endothelial* cells of different organs including the Kupffer cells which are

found in the sinusoids of the liver The parenchymal liver cells apparently have nothing to do with bilirubin formation and extrahepatic tissues probably play a more important role in bile pigment formation than the Kupffer cells After it is formed bilirubin is brought by the blood stream to the liver where in passage through the hepatic capillaries it is selectively removed from the blood by the epithelial liver cells and is excreted into the bile canaliculi whence it passes mixed with the rest of the bile through the larger bile ducts into the duodenum

The mechanism by which bile pigment leaves the blood stream to enter the liver cells for excretion is not definitely known It is possible that from the standpoint of bilirubin excretion the hepatic lobule may be divided functionally into two major zones and an intermediate zone The acceptance zone is that portion of the lobule in which the Kupffer cells take up bilirubin and pass it on to the underlying hepatic parenchyma In the intermediate or conversion zone the originally acidic pigment is converted through neutralization with alkaline bile salts elaborated by the liver into bilirubinate which renders the pigment water soluble The central portion of the lobule serves as the excretion zone in which bilirubin enters the bile canaliculi from the parenchymal liver cells and then passes as a bile constituent to the periphery of the lobule and into the hepatic ducts

The cycle of bilirubin formation from hemoglobin and its transport by the blood stream of the liver which abstracts it from the blood and excretes it with other constituents of the bile is a never ending process It is obvious that in order to prevent accumulation of excess bile pigment in the blood the liver cells have to be capable of excreting efficiently the bilirubin brought to them by the blood stream On the basis of the above-mentioned physiological facts several at least theoretically plausible circumstances present themselves for consideration as possible causes of jaundice Thus jaundice would occur

(1) If there were mechanical obstruction to the outflowing of bile through the ducts
(2) If the threshold of the liver for bilirubin excretion became markedly raised

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(1) If there were mechanical obstruction to the outflowing of bile through the ducts.
(2) If the threshold of the liver for bilirubin excretion became markedly raised

(3) If bilirubin were produced faster than the normal liver cells could excrete it

(4) If the excretory mechanism of the liver became so deranged that the amount of bilirubin normally produced could not be satisfactorily removed from the blood

(5) If there occurred any combination of the above conditions

The first condition mentioned was also the first to be recognized as a cause of jaundice both by pathologists and clinicians Obstruction of the common bile duct by a gallstone impacted in the ampulla of Vater by carcinoma in the same location or by extrinsic *compression of a neoplasm in the head of the pancreas* which bears an intimate anatomical relation to the terminal end of ductus choledochus—each constitutes an obvious reason for jaundice Extrinsic pressure by the hilar lymph nodes or carcinomatous gall bladder can be added to the list All these conditions are examples of extrahepatic obstruction that is obstruction of the larger ducts of the biliary system outside of the liver However obstruction may *also take place in the smaller channels (biliary canaliculi) confined* to the liver substance itself Were these changes diffuse enough to involve a sufficient number of bile canaliculi such occlusion may attain significant proportions and become at least a contributory factor in producing jaundice This type of blockage commonly referred to as intrahepatic obstruction usually takes place as a part of the composite picture of pathological processes occurring in liver disease The recognition of intrahepatic occlusion as a factor in pathogenesis of certain types of jaundice represents a more recent advance in our knowledge of the different mechanisms of icterus production than the appreciation of the more obvious case of gross extrahepatic occlusion

It was not long before the early pathologists learned from their gross dissection that while there were some cases of jaundice in which a mechanical obstruction to the outflow of bile through the extrahepatic bile ducts could be easily demonstrated there were many other instances in which no such obstruction was to be found Such cases were grouped together under the term nonobstructive jaundice Possibilities (2) (3) and (4) belong in that class along with some conditions in (5)

The second factor mentioned namely a significant elevation of

the threshold of the liver for bilirubin excretion is rather hypothetical and probably does not actually exist apart from a single clinical entity known (congenital non hemolytic icterus)

The third possible condition i e an uncomplicated excessive production of bilirubin is probably not in itself sufficient to give rise to jaundice in the absence of other complicating factors In the first place conditions of excessive production of bilirubin are frequently associated with other factors that impair the excretory power of the liver In the second place the liver has a remarkable reserve power and is able in health to excrete much more bilirubin than is ordinarily delivered to it even though a small amount of bilirubin is retained normally in the blood after the manner of threshold substances There is apparently a considerable excess of liver tissue above the amount necessary for the performance of its various functions including the function of bilirubin excretion Although removal of the entire liver from the dog invariably results in jaundice with removal of as much as 95 per cent of the liver substance the remaining liver tissue will suffice to prevent the development of icterus The same condition obtains in clinical practice Considerable amounts of liver tissue may be rendered functionless by a disease process without jaundice Thus the fact that the liver possesses a much greater capacity for excreting bilirubin than it is called upon to use normally makes it clear that excess of bilirubin in the blood stream will be taken care of without the development of icterus This is evidenced by a number of pathological conditions in which the amount of pigment in the stool is greatly increased above normal signifying an increase in amount of bilirubin produced and excreted yet jaundice is conspicuous by its absence It is possible that when bilirubin is produced in excessive amounts over prolonged periods of time like in congenital hemolytic icterus the continued strain upon the liver may conceivably impair its ability to excrete However the question remains whether or not increased demands upon the liver actually produce such a state of functional exhaustion In fact the reverse may be true *i e upon a demand for increased work the liver responds by an increase* in efficiency through the process of work hypertrophy At any rate should an impairment of function actually result from over work this would introduce another factor in causation of jaundice in addition to uncomplicated excess bilirubin production impair

ment of the power of the liver to excrete Under such circumstances jaundice would be produced through the operation of both factors of overproduction of pigment and impairment of liver function This would support the view that uncomplicated overproduction of bilirubin in itself is not conducive to the development of icterus

The fourth possibility is that of a disturbance in the excretory mechanism of the liver to such an extent that the amount of bili rubin produced normally cannot be excreted This actually occurs in clinical practice It is important to point out that a mere func tional depression of the excretory power of the liver will hardly ever be sufficiently acute to interfere with bilirubin excretion to the extent of producing clinical jaundice However if the total amount of the functioning liver tissue is reduced through pathological proc esses of necrosis and cellular damage jaundice will supervene when ever the amount of tissue rendered functionless by disease assumes such proportions that the amount of tissue remaining alive is insuffi cient for the proper removal of bilirubin from the blood

As to the last possibility mentioned (5) there is a great deal to be said regarding the production of icterus by a combination of factors that when operating singly are not in themselves sufficient to give rise to clinical jaundice While neither the overproduction of bilirubin alone nor the mere functional depression of the excretory ability of the liver is sufficient to produce icterus the joint oper ation of these factors may lead to the development of that condition Whereas the liver with a reduced capacity for excreting bilirubin may be able to clear the blood of the pigment formed normally if the pigment is produced in excess it may be unable to excrete it all and jaundice will result from the retention of the excess bili rubin Such a situation has actually been known to arise in clinical practice for the conditions responsible for increased production of bile pigment are frequently associated with the factors depressing the excretory function of the liver Jaundice then results by virtue of the fact that a liver with depressed excretory function and reserve power is called upon to excrete the pigment produced in excess To recapitulate what has been said above the production of jaundice will be dependent upon the balance between the amount of bili rubin formed and delivered to the liver for excretion and the capacity of the liver to excrete it

Taking a large view of jaundice as caused by a multitude of different pathological conditions the mode of its production can be

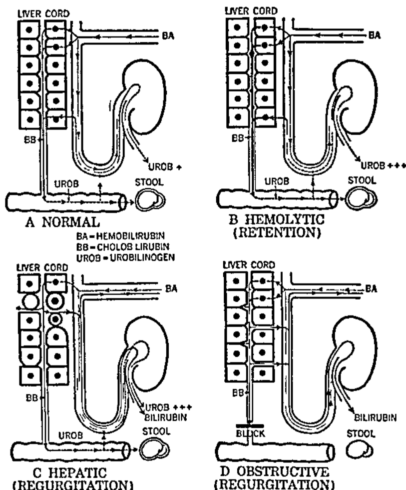


Fig 7 Schematic drawing explaining the changes of the bile pigment metabolism in the various forms of jaundice From F Steigmann H Popper and K A Meyer Courtesy of *J A M A*

reduced to a consideration of two fundamental processes Irrespective of etiology all the various forms of icterus can be divided into two distinct groups from the point of view of the essential mechanism responsible for its production These are (*a*) retention

jaundice and (*b*) regurgitation jaundice In the first group belong all cases in which the liver is functionally unable to remove from *the blood the bile* pigment produced in excess Bilirubin then accumulates in the blood stream and diffuses into the various tissues and skin where it is recognized as the indicator of disease In the second group icterus ensues upon the escape of the whole bile from bile canaliculi into the blood stream This can occur (1) as a result of obstruction to the outflow of bile through the ducts (mechanical obstruction) or (2) because of disorganization of the normal architecture of the diseased liver disruption of the liver cords through necrosis of the individual liver cells leads to the establishment of abnormal communications between bile canaliculi and blood channels and thus allows bile to regurgitate into the blood stream Hemolytic jaundice is due to excessive destruction of red blood cells with the release of great amounts of bilirubin into the blood stream and therefore belongs to the first type (*a*) The second group (*b*) comprises the cases of mechanical obstruction of the extrahepatic bile ducts (obstructive jaundice) and cases of liver damage (parenchymatous hepatogenous or hepatocellular jaundice)

Parenchymatous or hepatogenous jaundice is usually considered to represent a nonobstructive type of icterus However it must be remembered that in some instances of liver involvement (hepatitis) there is an added factor *of intrahepatic obstruction This arises from* parenchymal damage which leads to necrosis and dissolution of liver cell cords disrupting the continuity of the biliary canaliculi and resulting in biliary stasis with bile thrombi (See Fig 10 p 52) Another mechanism of microscopic biliary obstruction is localized in the periportal spaces where exudate may compress the canals of Hering the most vulnerable part of the biliary system In still other cases of liver involvement the parenchymal liver cells escape the damage altogether the principal lesion being pericholangitis and bile thrombi in the finer biliary radicles The differential diagnosis between extrahepatic obstructive jaundice and hepatogenous type is rendered more difficult by the fact that intrahepatic disease presents obstructive aspects

Behavior of Bile Pigment and Bile Salts in Various Types of Jaundice

The classification of icterus into regurgitation and retention types has a sound basis not only from the standpoint of the mechanism of its production but also with regard to certain clinical laboratory findings These will now be discussed briefly and correlated with the two types of jaundice

Direct and Indirect Reacting Bilirubin

Although the original source of bilirubin found in the blood serum in health and disease (jaundice) is the same there are two kinds of pigment found in the plasma of jaundiced patients with one or the other kind predominating depending upon the type of icterus and mechanism of its production There is in the first place bilirubin present in very small amounts in the blood serum under normal conditions for the reason that it is removed from the blood stream by the liver parenchymal cells in the manner of a threshold substance* It is the same bilirubin that is found in excess in retention type jaundice Secondly in the regurgitant type of icterus most of the bilirubin in the blood stream is the pigment that has once passed through the liver cells into the bile canaliculi but that subsequently found its way back into the blood because of obstruction of the ducts (obstructive jaundice) or because of necrosis of the liver cells leading to establishment of abnormal communications between bile canaliculi and blood channels (parenchymatous jaundice)

The van den Bergh test—which is a modification of Ehrlich's diazo reaction—is the laboratory procedure employed for the detection of bile pigment in blood serum A great merit of the test lies not only in the fact that it can be used for quantitative measurement of the pigment when present in the plasma in even minute amounts but also in that it distinguishes between the two kinds of bilirubin

There are two main types of this reaction—the direct and indirect The direct one occurs without the addition of alcohol which is

* A threshold substance in relation to its excretion by either kidney or liver is a substance that has to be present in the serum over a certain critical level before it becomes excreted

essential for the indirect type of reaction Whether the van den Bergh test gives results of one type or another will depend upon the nature of bilirubin present In retention jaundice the *pigment gives* the indirect reaction, while in regurgitation jaundice the reaction is *direct In other words, the type of reaction* depends entirely upon whether or not bilirubin has passed through the parenchymal liver cells The reason for this is not entirely clear According to one view, bilirubin removed from the blood by the liver cells is changed in some way within those cells before being excreted into the bile or regurgitated into the blood stream Another *view is that more* probably the pigment is not changed by the liver cells, but that in the bile some substance is present that is responsible for the dif ference in reaction In other words, the type of reaction depends upon the medium in which the bile pigment is contained, rather than upon the alteration of the pigment itself Thus, while pure bilirubin at the pH of the blood gives the direct or prompt reaction, *if it is added to normal plasma it gives the indirect reaction Such* behavior is believed to be due to the adsorption of bilirubin by the plasma proteins this union preventing the pigment from reacting promptly with the diazo reagent, addition of alcohol is necessary to break up the link between the two and thus allow the pigment *to react with the reagent (indirect reaction) If, however, substances* having the property of lowering surface tension are added to the plasma together with bilirubin the reaction of the pigment remains direct apparently because substances that lower surface tension seem to be adsorbed by the plasma proteins more readily than is bilirubin *and therefore* the pigment remains free Bile salts and cholesterin are particularly potent in preventing the adsorption of bilirubin by the plasma proteins *Significantly enough, both sub* stances are present in the whole bile and therefore also in the blood whenever bile leaks back into the general circulation, as in regurgi tant type of jaundice, in which the van den Bergh reaction is direct When a solution of pure sodium bilirubinate, which gives a direct *reaction is added to normal serum an* indirect reaction is obtained However, if bile salts, sodium oleate, or cholesterol are added to the serum together with the bile pigment the reaction becomes *direct* Also when the bile salts concentration in the blood is elevated the serum may give a direct reaction, though the serum bilirubin is

jaundice may present only evidence of icterus in the sclerae without distinct discoloration of the skin whereas a patient with hepatitis or common duct stone will have well pronounced generalized jaundice

Bile Salts

Another point of clinical significance is that bile salts also filter readily through the kidneys so that in the regurgitant type jaundice where the whole bile gains access to the general circulation bile salts in addition to bilirubin are recovered in the urine whereas in the retention type of jaundice bile salts are absent in both the blood and the urine unless there be a complicating factor of an associated involvement of the liver and/or biliary tract

Thus in the retention type icterus there results so-called dissociated jaundice pigment is present in increased amounts in the blood in the absence of bile salts The French School is responsible for the original observation that for some unknown reason certain cases of regurgitant jaundice may also be of the dissociated type For example in non jaundiced patients with cirrhosis of the liver occasionally there may be itching of the skin and bradycardia phenomena believed to be due to retention of bile salts But here we need not be greatly concerned with these exceptions

Under some conditions the plasma may retain a large amount of bile pigment without any of it appearing in the urine or tissues as if the blood not willing to yield any of it to the tissues held the pigment firmly in its grip Hence the striking disparity sometimes seen between icterus of the plasma and icterus of the skin The reason for this is not known

Urobilinogen

In retention jaundice while bilirubin is absent from the urine its by product urobilin will be found there in increased amounts The reason is obvious In this type of jaundice there is usually excessive blood destruction resulting in extensive bilirubin formation The stools contain an increased amount of bilirubin (and urobilin) because in the face of the increased production of this pigment the liver is excreting more of it than under normal conditions even though it cannot excrete enough of the excess to prevent jaundice As a result more urobilin is reabsorbed into the circula

by simple reduction is responsible for the delayed or indirect reaction and bilirubin only for the prompt *direct reaction*

Another important distinction between the two types of bilirubin from a clinical standpoint is the differentiation on the basis of dialysis through membranes and its relation to renal filterability Although the difference in the dialyzability of the two types of pigments is denied by some the fact remains that clinically such difference does exist so that while urine usually contains bilirubin when the pigment in the blood gives a direct van den Bergh reaction (cholobilirubin) it is free of bilirubin when the plasma gives an indirect reaction (hemobilirubin) Thus in retention icterus bilirubinuria does not occur (acholuric jaundice *) whereas when the serum gives a direct reaction (regurgitation icterus) bilirubinuria occurs (choluric jaundice) Bilirubinuria is observed whenever the direct reacting pigment reaches a concentration of about 2 mg per cent and not infrequently at even lower levels The kidneys are impermeable to indirect reacting bilirubin at all times Although there has been certain opposition to this view with few exceptions it retains its practical significance and for purposes of clinical practice may be considered as an infallible rule *It is not yet entirely clear* just why only the direct reacting bilirubin can escape readily from the blood into the urine *Whether the close affinity of the indirect* type of pigment for the plasma proteins or its relative insolubility in water is responsible *for its lack of filterability through the glomerular* filter remains a moot question By contrast the direct reacting bilirubin being present *in the form of an alkali salt is water soluble* Whatever the reason for the difference in behavior of the two types of bilirubin *in relation to kidney filterability the fact remains that* clinically this distinction can be readily recognized.

The same difference in filterability may also be responsible for the clinical observation that shows that in retention jaundice the pigment must *reach considerably higher concentration in the blood* than in the regurgitation type to give rise to the same degree of discoloration of the skin *That is with the same concentration* of bile pigment in the serum the jaundice is more intense in patients with regurgitant type *icterus than in the retention type* With the same degree of icterus of the plasma a patient with congenital hemolytic

* Acholuria means absence of bile pigment in the urine

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and urine and urobilin is found in the urine and feces in increased amounts (urobilinuria) in regurgitant jaundice the pigment gives a direct reaction in the serum and is found in the urine (bilirubinuria) along with the bile salts and urobilin may be either totally absent or present in increased amounts in the urine and absent or diminished in the stool

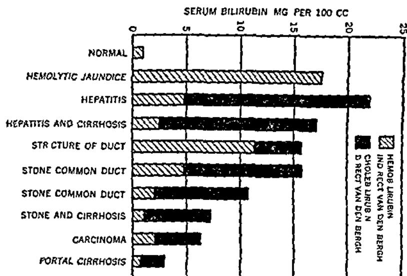


Fig 8 The distribution of the two types of bilirubin in the serum in an illustrative series of cases of jaundice After C H Greene M Plotz and S A Localio Courtesy of *Arch Int Med*

In retention jaundice bilirubin present in the serum is not all necessarily of the indirect type Some of it may give a direct van den Bergh reaction because of the associated liver damage Conversely in regurgitation jaundice not all the bile pigment present in the serum is necessarily direct reacting bilirubin some indirect bilirubin may also be present There are two reasons for this in *the first place bilirubin is a threshold substance in health the pigment* is found in the blood in small amounts as indirect bilirubin In the second place with impairment of liver function in hepatitis some of the pigment that accumulates in the blood is not only that regurgitated back into the circulation from bile canaliculi but also some that the malfunctioning liver failed to clear from the blood and excrete into the bile More will be said about this later

tion which brings it back to the liver for re excretion in the bile However since in hemolytic jaundice the liver s excretory power may be impaired the organ fails to remove all of the urobilin from the blood stream and the balance of it is excreted in the urine On the other hand in regurgitation jaundice the stools contain less bilirubin and urobilin than usual because the passage of bilirubin to the intestine is interfered with either by obstruction of the ducts or by liver necrosis associated with rupture of the biliary canaliculi which allows bile to leak into the blood stream When the obstruction is complete none of the bile pigment can enter the intestinal tract both bilirubin and urobilin will be absent from the stool and no urobilin will be recovered from the urine In the presence of incomplete obstruction some bile reaches the intestine and a small amount of urobilin is formed The diseased liver however may not be capable of removing from the blood even urobilin presented to it for re excretion in smaller than normal amounts so that an increase in urinary urobilin may be detected

SUMMARY

To summarize the evidence presented above whereas in retention jaundice the bile pigment gives an indirect reaction in the serum and is absent from the urine the bile salts are absent from the blood

TABLE IV

THE DIFFERENCES BETWEEN THE CLINICAL LABORATORY FINDINGS IN THE TWO MAIN TYPES OF JAUNDICE

	Blood—van den Bergh	*Urine*			*Faeces—Urobilin*
		Bilirubin	*Bile Salts*	*Urobilin*	
Retention (acholuric) Jaundice	indirect	o	o	+	increased
Regurgitation (choluric) Jaundice	direct	+	+	o +	decreased or absent

After Rich

panied by anoxemia due to anemia from excessive hemolysis (hemolytic icterus) or to poor oxygenation (pneumonia heart failure)

It has been noted that in instances of severe and long standing anemias there is an atrophy of the central portion of the liver lobules more or less proportional but not necessarily so to the severity and duration of anemia The same atrophy has also been produced experimentally by simple hemorrhage On autopsy shrinkage of the liver cells about the efferent veins was noted to be marked so that consequent widening of the capillaries in the affected areas produced the appearance characteristic of chronic passive congestion Atrophy of the central portion of the liver lobules is known to occur in chronic passive congestion of cardiac decompensation The fact that an exactly similar lesion accompanies both severe anemia and chronic passive congestion led to the belief that the underlying cause of atrophy in both conditions was anoxemia This is substantiated by the finding of the same lesion on subjecting experimental animals to an atmosphere with reduced oxygen tension

Experimental evidence has been presented to the effect that anoxemia depresses excretory function of the liver However because of the great reserve power of the organ anoxemia alone is unable to produce sufficient retention of bilirubin in the blood to result in clinical jaundice There must be present the added element of increased blood destruction Both these factors may exist in pneumonia That anoxemia may well be an accompaniment of such pathological process in the lung is only too well recognized A moderate bilirubinemia without clinical jaundice occurs in every case Abundant iron deposits in the pneumonic lung have been observed suggesting a hemolytic process Bilirubin is formed by the intrapulmonic destruction of the hemorrhagic exudate in the alveoli and is resorbed into the circulation The same set of conditions (anoxemia and increased bilirubin production) may also be present in the chronic passive congestion of heart failure Anoxemia in such cases is quite obvious In addition there is increased blood destruction within a congested lung and especially in infarcted areas

Febrile states also have a depressing influence on liver function Morphological alteration of the epithelial cells in various organs designated by the term cloudy swelling is generally known to occur during febrile illnesses It is a temporary change from which com

Classification of jaundice into retention and regurgitation types helps a great deal in general orientation It is worth while there fore to examine a little more closely the two groups with regard to the conditions constituting them and the existing pathological lesions

PATHOGENESIS OF RETENTION TYPE JAUNDICE

This type of jaundice usually results from overproduction of bile pigment coupled with some functional liver disturbance While the normal liver is able to cope with excessive amounts of bilirubin brought to it by the blood stream abnormal conditions in this organ may interfere with excretion of bilirubin even when pro duced in normal amounts The latter situation gives rise to the *retention type of jaundice in some individuals in whom there is* a constitutional hepatocellular inferiority in bilirubin excretion The condition may or may not be familial It has been described under various names and by different investigators intermittent juvenile icterus constitutional hyperbilirubinemia or constitutional hepatic dysfunction and familial non hemolytic jaundice The ab normality is characterized by simple accumulation of bilirubin of the indirect reacting type This condition is quite rare

Liver dysfunction similar to that described above may be acquired as a result of virus and other infections or from various poisons (arsenicals sulfonamides etc) It has been noted that coryza may interfere with normal liver function The mild retention icterus thus produced may *become more marked with developing evidence* of regurgitation jaundice as the pathological process proceeds be yond a mere depression of hepatic function into the stage of anatomi cal changes in the liver Or it may recede without this

Two factors enter into the consideration of common conditions *giving rise to retention jaundice* These are increased *bilirubin* production and hepatic impairment both are frequently the result of one and the same underlying pathological process The first factor increased bilirubin production is the by product of increased blood destruction The second factor liver involvement is related to (1) anoxemia and (2) febrile states Conditions giving rise to increased bilirubin production through blood destruction are usually accom

hemoglobin with a tendency of the initial polycythemia to disappear Simultaneously the bilirubin content of the blood rises as a result of the rapid destruction of excess hemoglobin present in the circulation at the time of birth Added to this is evidence of a subnormal excretory power of the liver as shown by the inability of the organ to excrete properly the various dyes used to test its excretory function This deficient excretory power may be simply the result of immaturity which soon disappears along with the icterus

In hemolytic anemias marked blood destruction leads to excess bilirubin formation and anoxemia of an anemic state the latter exercising a depressing influence on hepatic function The damage of liberated hemoglobin to the liver cells may be an added factor in impairing their efficiency to excrete bilirubin Jaundice however by no means invariably occurs in some of these conditions (paroxysmal hemoglobinuria for example) and whether or not it does occur depends not only on the degree of hemolysis but also on the initial level of red blood cells It is more likely to occur in patients who have already been rendered anemic by previous attacks so that *finally when severe anemia occurs the added factor of anoxemia* comes into play depressing the liver function sufficiently to produce jaundice However there are many patients with familial hemolytic icterus in whom jaundice is present in the absence of severe anemia There are two possible explanations Long continued chronic anemia of even a mild to a moderate degree may have the same effect on liver function as an acute and severe anemia of short duration Moreover it has been shown that hemolytic anemias are associated not only with an increase in bilirubin production but in certain instances also with obstruction of the finer bile channels in the liver Such obstruction may be due to the swelling of the liver cells or fibrin plugs and thrombi within the biliary canaliculi The poison that produces hemolysis can also cause precipitation of bile in the bile capillaries In other words an element of regurgitant jaundice is then added to the process of bile pigment retention

Pathogenesis of Regurgitation Jaundice

In this type of jaundice there is a leakage of bile into the blood It is not definitely known in all instances just how bile is resorbed from the liver into the circulation The manner in which jaundice

plete recovery takes place when the causal febrile condition has disappeared Kidney involvement by this process is *common and is* evidenced by transitory febrile albuminuria It is conceivable that various functions of the liver may be similarly involved the common occurrence of urobilinuria during fever bearing *testimony to that* effect While febrile disease and cloudy swelling in themselves are not sufficient to depress the excretory power of the liver to the point that jaundice will appear, when *such febrile state occurs in* conjunction with overproduction of pigment and anoxemia, the stage is set for the retention type of jaundice Thus, in hemolytic septicemias, in addition to the *depressing effect of febrile infection* upon the excretory power of the liver, there is excessive blood destruction along with anoxemia that goes with anemia A similar state of affairs obtains in later *stages of malaria, where all three* factors, i e febrile state, excessive destruction of erythrocytes, and *the depressing effect of severe anemia* come into operation *It is* believed that malaria always *produces some liver damage, sometimes* fatal In such instances jaundice may become intensified by hepatitis

A somewhat similar explanation holds in icterus neonatorum *During the first few days after birth, there occurs a* rapid fall in

TABLE V

PATHOGENESIS OF JAUNDICE

Jaundice will occur whenever there is a disturbance between the amount of bilirubin delivered to the liver for excretion and the capacity of the liver to excrete it This disturbance may supervene in the course of any one of the following conditions

(1) Excessive production of bilirubin through increased hemolysis coupled with impairment of the liver excretory function (Hemolytic jaundice)

(2) Impairment of the liver excretory function through a disease process *involving hepatic parenchyma even when bilirubin is produced in* normal amount (Hepatocellular or Parenchymatous Jaundice)

(3) Mechanical obstruction of the biliary system interfering with the flow of bile to the intestinal tract (Obstructive Jaundice)

In (1) jaundice is caused by retention of bilirubin in the blood stream (Retention Jaundice) Bilirubin is of the indirect reacting type

In (2) and (3) jaundice is caused by regurgitation into the circulation of bilirubin that has previously passed through the liver cells (Regurgitation Jaundice) Bilirubin is of the direct reacting type

3 Hepatic lesions
  a Neoplasm primary or secondary
  b Cyst
  c Abscess
  d Gumma
4 Enlarged lymph nodes in portal fissure
  a Metastatic malignancy
  b Inflammation
  c. Syphilis
  d Tuberculosis
  e Lymphoblastoma leukemia Hodgkin s disease
5 Gall bladder lesions
  a Carcinoma with invasion of common duct
6 Duodenal lesions
  a Gastro-intestinal catarrh

How the regurgitation of bile takes place in the absence of gross obstruction of the larger bile ducts has been a subject for debate and of considerable research The process must involve a rather profound disorganization of the normal architecture of the liver, which may occur as a result of liver damage from a multitude of causes

• Toxic changes in the liver cells result in degeneration and necrosis The intensity of jaundice may be severe even when necrosis and cell damage are not particularly widespread but of such an extent as to affect a sufficient number of liver lobules to reduce the functional reserve of the organ

Two different processes may be found taking place side by side in the damaged liver One is the injury to the parenchymal cells characterized by central necrosis and heavy infiltration with fat and bile pigment the presence of bile pigment in liver cells signifies damage since normally it is repelled and only necrobiotic cells store it Generalized involvement may lead finally to acute atrophy There is necrosis of the parenchymal cells that intervene between the bile *canaliculi and the Disse spaces The disruption of liver cell* cords creates abnormal communications between these spaces and the biliary canaliculi Bile escapes into the lymph channels and regurgitates through the thoracic duct into the jugular vein and general circulation

is produced by gross obstruction is more readily understood Such obstruction brings about dilatation and back pressure in all bile *ducts* with gradual and progressive extension into the bile capillaries There is *stagnation* of bile *and excessive pigmentation of* the liver cords and Kupffer cells Apparently bilirubin is excreted by the liver cells into the bile canaliculi which become distended with inspissated bile (capillary thrombi) and finally rupture thus permitting the escape of their contents into the lymph spaces of Disse thence to the thoracic duct and the blood The increased intrabiliary pressure probably damages bile canaliculi so as to result in increased permeability The appearance of jaundice may depend on other factors besides mere mechanical occlusion of the ducts Inflammation of the bile ducts may play a role Resorption of bile takes place only under considerable back pressure of about 20 mm Hg The conditions responsible for mechanical occlusion of the extrahepatic biliary passages are listed below

CAUSES OF GROSS MECHANICAL OBSTRUCTION

(Modified after Miller and Machella)

A Obstruction within the lumen of the ducts
- 1 Common duct stone
- 2 Parasites
  - a Ascaris lumbricoides
  - b Hydatid
  - c Hepatic distomiasis
    - (1) Clonorchis sinensis
    - (2) Opisthorchis felinens
    - (3) Fasciola hepatica
- 3 Mucous plugs and swelling of the duct wall
- 4 Stricture (congenital or secondary to cholangitis or trauma)
- 5 Neoplasm
- 6 Edema of the ampulla of Vater?
- 7 *Carcinoma of the ampulla of Vater*

B Obstruction by extrinsic pressure on bile ducts
- 1 Pancreatic lesions
  - a Carcinoma of the head of the pancreas
  - b Chronic pancreatitis
- 2 Duodenal lesions
  - a Tumor

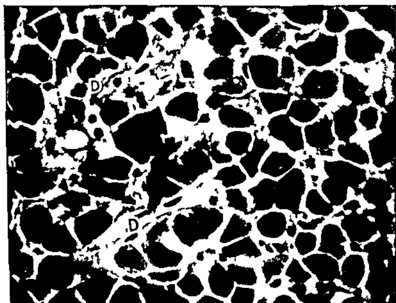


Fig 9 Marked dissociation of liver cells Note the rounding of the borders of the cells and the widening of the Disse spaces (D) After J D Kirshbaum and H Popper Courtesy of *Arch Int Med*

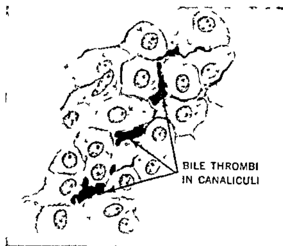


Fig 10 Drawing of a high power field showing bile capillaries distended with bile thrombi After F M Hanger and A B Gutman Courtesy of *J A M A*

The other process is represented by the damaging influence on the endothelial lining of the blood capillaries in the liver of the same toxin that injures the liver parenchyma The increased permeability of the sinusoidal walls allows protein rich fluid to escape from the capillaries into Disse spaces Proteins bind water and when lymphatic drainage is insufficient to carry away the escaped fluid edema results and the liver enlarges The fluid accumulates between the cords of the liver cells and finally destroys their structure The disorganization of the liver cords may thus be affected not only by direct action of the toxins on parenchymal cells but also by extracellular pressure The presence of edema fluid between the capillaries and the liver cells results in their undernutrition and suffocation as the diffusion of metabolic substances and oxygen from the capillaries to the cells is impaired (serous hepatitis) Simple serous hepatitis alone does not cause jaundice However when necrosis of the liver is combined with diffuse serous hepatitis the excretion of the regurgitated bile is impaired and jaundice results.

While the cellular necrosis produced by direct action of a toxin on parenchymal cells is responsible for shrinkage of the liver (atrophy) the capillary damage explains the enlargement of the organ Whether in a given case of hepatitis the liver shrinks or enlarges may possibly be dependent on the balance between the two pathological processes Acute or subacute yellow atrophy is the result of an extensive necrosis The extent of inflammatory reaction and venous engorgement also determines the size of the diseased liver

The liver damage described above may result from the action of a great variety of different chemical vegetable bacterial virus and protozoal poisons which are listed in the table below Some poisons like sulfonamides may produce jaundice by means of two different *mechanisms such as hemolysis* and/or liver damage In other words some of these agents act as either hemolytic or hepatic poisons or both

CHEMICAL POISONS

Alcohol
Arsphenamine
Arsenic
Carbon tetrachloride
Chloroform

Cinchophen
Phosphorus
Sulfanilamide
Tetrachlorethane

VEGETABLE POISONS

Mushrooms (Amanita muscaria and phalloides)

BACTERIAL AGENTS

Spirochete ictero hemorrhagica
Spirochete pallidum
Streptococcus
Gonococcus
Gas bacillus
Paratyphoid
Other organisms and toxins such as occur in pneumonia peritonitis hemolytic streptococcus septicemias meningococcemia and other severe toxemias

VIRUS AGENTS

Virus of yellow fever
Virus of infectious hepatitis or catarrhal jaundice

Pathological Manifestations of Jaundice

Clinical jaundice makes its appearance whenever the concentration of bilirubin in the blood exceeds the level of about 1 3 mg per cent While some tissues stain deeply others do so only slightly or not at all It seems that some tissues have a predilection for the imbibition of bile pigment It may be that the presence of elastic fibers is a determining factor so that parts of organs rich in them stain deeply Usually the body secretions cartilage cornea and cerebrum (except in icterus gravis infantum) do not imbibe bilirubin

Jaundice appears first on the sclerae next on the face and last on the trunk Extremities are seldom deeply colored At first there is more bilirubin in the blood than is apparent in the skin However once the tissues become stained they remain so after the bilirubin content of the blood diminishes and occasionally even after it has returned to normal

of hepatic insufficiency on the organism and the precise and im mediate causes of hepatic coma remain unknown to date

The effect on the kidney the so-called hepato renal syndrome (bile nephrosis) is probably due to cytotoxic changes in the renal tissue produced by excreted bile salts and other toxic factors Under the name of hepato-renal syndrome is recognized a certain trend of clinical and laboratory findings that reflect renal changes inci dental to hepatic injury with or without jaundice The kidney is second only to the liver as an important excretory and detoxifying organ In some instances of liver insufficiency with progressive fail ure the kidneys attempt to compensate for hepatic failure at excre tion and detoxification While they may succeed in some measure at first sooner or later the renal function also fails because the kid neys are not fitted to handle many of the products of hepatic metabo lism and the toxic elements liberated in either the normal or dis eased liver As a result the renal mechanism finally deteriorates This failure of renal function may play an important and frequently decisive role in bringing about a rapid downhill course and ulti mate dissolution It cannot be determined just how far the hepatic disturbance must progress before clinical evidence of renal involve ment (hepato-renal syndrome) makes its appearance It may occur in the absence of jaundice This circumstantial evidence can be used as a rough measure of the degree of hepatic disturbance both from an anatomical and functional standpoint Under the circum stances any significant change in the kidney could be employed therefore in properly selected cases other things being equal as a measure of the preceding clinically recognizable disturbance in the liver Frequently urinary findings simulating nephritis are present Various degrees of oligura occur but never a complete anuria Formed elements may be found in the urine With progression of renal disturbance there results nitrogenous retention in the blood At times azotemia is the first indication of an aggravation of the primary liver disease and the level of the increased azotemia paral lels the severity of the disease as a whole

With regard to hepato renal syndrome two symptom complexes have been distinguished one characterized by sudden onset of hyper thermia delirium and coma the second by renal failure and uremic death as described above An episode of circulatory collapse or other shock like state often precedes the last mentioned symptom complex

Irrespective of the mechanism by which icterus is produced, its effect on the organism is dependent upon three factors (1) retention of the constituents of bile in the blood and tissue fluids, (2) absence of bile from the intestinal tract, and (3) liver damage Of the constituents of bile that infiltrate the various tissues, bile salts are the most significant Bile acts adversely on the vascular, nervous, renal, and cutaneous systems

The bradycardia not uncommonly found in association with jaundice is probably due to bile salts In moderate doses they increase vagal inhibitory tone The same vagal effect can be produced reflexly by distention of the biliary passages

Bile salts administered intraspinally (in cats) produce motor and sensory disturbances and even death from respiratory paralysis However, clinically there is very little evidence that the mental symptoms and the picture of hepatic coma with all its manifestations such as mental depression, irritability, headaches disorientation, delirium, and convulsions are due to the bile retention *per se*

Bile salts may produce some hemolysis of the red blood cells Thus, even in obstructive jaundice, blood destruction may serve as a contributory factor in the production of icterus It is possible that jaundice and/or associated conditions may adversely influence hemotopoiesis

The absence of bile salts in the intestinal tract interferes with digestion and absorption of fats and fat soluble principles (vitamins A, D, and K) The body then may lose a substantial amount of fat daily The fat in the stool, normally constituting about 15 per cent of the excreta may increase to 80 per cent being present chiefly as fatty acid crystals The unavailability of vitamin K is responsible for cholemic bleeding tendencies There is also interference with *calcium absorption, resulting in a significant alteration* in the blood calcium concentration

Deficient absorption of calcium and vitamin D may be responsible for osteoporosis observed in some patients with long standing obstructive jaundice Pruritis is probably due to the irritating effect of bile salts on the cutaneous nerve endings

The most important result of liver damage is the interference with *metabolic functions of this organ*, which plays such an important role in the body economy However, the exact consequences

Mann F C et al *Am J Physio* 109 393 1924
Mann F C and Bollman J *J A M A* 104 371 1935
Meulengracht E *Klin Wchnschr* 18 118 1939
Ohno Y *Munchen Med Wchnschr*, 78 1639 1931
Rich A R *Bull Johns Hopkins Hosp* 36 233 1925
Rich A R *Bull Johns Hopkins Hosp* 47 338 1930
Rich A R and Resnik W H *Bull Johns Hopkins Hosp* 38 75 1926
Rosenthal F *Klin Wchnschr* 9 1909 1930
Schrager V L and Ivy A C *Surg Gynec and Obst* 47 1 1928
Steigmann F and Popper H *Gastroenterology* 1 645 1943
Thorn D S *McGill M J* 14 235 1945
Van den Bergh A A H *Der Gallenfarbstoff in Blu e* Leyden 1918
Watson C J *New England J Med* 227 705 1942
Wilenski A O *Arch Surg* 38 625 1929 *J Internat Coll Surg* 7 50 1944

Evidence of a renal component in the first syndrome is minimal and consists of vaguely described non specific changes of kidney structure such as cloudy swelling or of bile nephrosis in cases accompanied by jaundice In the second syndrome degenerative changes of greater severity have been usually noted

Strictly speaking a distinction must be made between the so-called hepato renal syndrome and bile or cholemic nephrosis The former is rather ill defined whereas the latter is well recognized Bile nephrosis is associated with more or less prolonged jaundice and is characterized by tubular degeneration often of a reversible nature and the presence of bile casts Bile salts are assumed to be injurious to renal epithelium and are believed to constitute the primary cause of degenerative damage Clinical studies of renal function in jaundiced patients demonstrate renal impairment and also its reversible nature It is agreed that simple bile nephrosis does not explain the severe renal insufficiency of the hepato-renal syndrome

BIBLIOGRAPHY

Barron E S G *Medicine* 10 77 1931

Bloom W *Bull Johns Hopkins Hosp* 34 316 1923

Cantarow A Dodek S and Gordon B *Arch Int Med* 40 129 1927

Colangiuli A *Arch d pat e clin med* 18 105 1938

Collinson G A and Fowweather F S *Brit Med J* 1 1081 1926

Coolidge T B *J Biol Chem* 132 119 1940

Dameshek W and Singer K *Arch Int Med* 67 259 1941

Elton N W *Am J Clin Path* 5 40 1935

Eppinger H *Leberkrankheite* Wien Julius Springer 1937

Hanger F M and Gutman A *J A M A* 115 263 1940

Hoover C F and Blankenhorn M A *Arch Int Med* 18 289 1916

Horrall O H and Carlson S J *Am J Physiol* 85 591 1928

Jordan F M and Greene C H *Am J Physiol* 91 409 1930

Karsner H T *Human Pathology* Philadelphia J B Lippincott Co 6th ed 1943

Kirshbaum J D and Popper H *Arch Int Med* 65 465 1940

Kugel M A and Lichtman S S *Arch Int Med* 52 16 1933

Lepehne G S *Ergebn inn Med u Kinderh* 20 221 1921

Lichtman S S *Disease of the Liver Gallbladder and Bile Ducts* Philadelphia Lea & Febiger 1942

Lichtman S S and Stern E L *Proc Soc Exper Biol and Med* 32 1201 1935

McMaster P D Broun G O and Rous P *J Exper Med* 37 395 1923

McMaster P D and Rous P *J Exper Med* 41 719 1925

liver and the diagnostic procedures used as aids in the differential diagnosis of jaundice For the latter purpose not all liver function tests are suitable while on the other hand not all laboratory diag nostic procedures are really tests of liver function

The term liver function test unfortunately acquired a connota tion not commensurable with its true significance and the facts it reveals The term implies that any particular test gives results that may serve as a measure of the functional state of the liver The fallacy of such a presumption is obvious in the light of our knowl edge which reveals marked constitutional variations in hepatic activity both in health and disease There can be marked variations in liver function from one patient to another suffering from the same type of hepatic involvement anatomic changes in the liver similar in nature and extent may exhibit rather marked differences in degree and type of functional impairment The manifold activi ties of the liver are variously disturbed in different diseases and in different individuals They are seldom affected to an equal degree Some of the tests may give normal readings when both clinically and pathologically advanced liver disease is present whereas others may register very poor function when actually the clinical course of the disease and the anatomic state of the liver are pointing in a favorable direction However one should not feel entirely discour aged in the face of all these complicating factors for any one single hepatic function can be expected to be disturbed in proportion to the extent and severity of the disease This offers the possibility of a quantitative index of hepatic disturbance The various activities of the liver are more or less closely interrelated so that impairment of one may adversely affect the others Still it would be more ap propriate to designate each laboratory procedure testing some spe cific hepatic activity not by the general term liver function test with all its broad implications but rather by the name of the specific function tested This would help one to keep in mind the limita tions of any single test employed It is only in the light of knowl edge of these limitations that a proper evaluation can be rendered of the results obtained Thus a certain procedure may test a meta bolic function and another an excretory one Again among the metabolic tests there are some for example that test the glycogenic ability of the liver (galactose test glucose test etc) and others that test the power of synthesis (prothrombin test) Among proce

DIAGNOSTIC PROCEDURES

WHEREAS in some cases of jaundice the diagnosis can be made readily on the basis of the history and physical findings, in many instances it is very difficult The attending physician then has to resort to complicated laboratory procedures, and even with their aid may fail to arrive at a satisfactory solution of the problem confronting him

The laboratory *procedures* available for the study of jaundiced patients include (1) qualitative and quantitative van den Bergh reaction (2) qualitative and quantitative estimations of bile pigment derivatives in the urine and feces, (3) liver function tests, (4) hematological and certain blood chemistry findings (5) cholecystography (6) duodeno biliary drainage, and (7) hepatolienography In selected patients a minor surgical procedure (peritoneoscopy) may be resorted to for diagnostic purposes Finally, in some instances only at laparotomy or necropsy can a definite diagnosis be made

There is no single miracle test available that will unravel the intricate problem in every case and give a ready made solution—at least not at the present state of our knowledge Such an ideal situation hardly exists in any other field of medicine and *there is no* reason to expect that the group of conditions under discussion be an exception The demand for a single universal test would be unreasonable The liver is so versatile in its activities that a common denominator for the test of its numerous functions can hardly be expected to exist

The large number of clinical laboratory procedures in use for evaluation of the functional status of the liver bears testimony to the fact that no single procedure is in itself entirely reliable, all inclusive, or diagnostic The physician must therefore choose from the array of tests available those best suited to a given case A distinction must be drawn between tests of the functional state of the

growth average values are usually higher 20 to 30 mg per cent fluctuations seldom occur and jaundice is persistent In parenchymatous disease of the liver the degree of icterus is variable It may be very mild but on the other hand some of the highest concentrations of serum bilirubine encountered (up to 70 mg per cent) are seen in severe forms of liver disease (acute atrophy) Whenever similarly high concentrations are found in obstructive jaundice an associated hepatic damage may be suspected In hemolytic icterus levels from 5 to 35 mg per cent are encountered

In parenchymatous jaundice the van den Bergh reaction may be indirect early in the disease during the initial stage of mere functional impairment of the liver As the disease progresses anatomical changes develop and widespread cellular necrosis may take place Intrahepatic obstruction mounts and as the bile begins to leak into the blood stream the van den Bergh reaction becomes biphasic and then direct During convalescence the reaction may change again to biphasic and eventually to indirect and negative

The qualitative van den Bergh test is of value in confirming *hemolytic icterus i e when a positive test for the indirect type of* bilirubin is obtained and a negative test for the direct type It fails to distinguish between obstructive and parenchymatous types of jaundice as the reaction is positive direct in both The positive direct reaction may even be encountered in cases of hemolytic icterus complicated by hepatitis or pigment calculi which the patients with chronic hemolytic anemias are so prone to develop On the other hand there is also present a varying amount of indirect bilirubin in serums that give a direct reaction This may be due to the fact that the hemolytic process plays a larger role in the pathogenesis of all types of jaundice than is commonly realized In fact pure or uncomplicated types of jaundice are not seen too frequently particularly when the condition has existed for some time The mixed type of jaundice is a common occurrence

Serial quantitative determinations of bile pigment showing daily fluctuations in the serum content of bilirubin may have both diagnostic and prognostic values They aid in distinguishing between obstructive jaundice of benign or malignant origin and hepatitis by demonstrating whether or not the icterus remains at a stationary level Such fluctuations cannot be as promptly and accurately determined by means of simple clinical observation The quantitative

tative determination of the indirect and direct reacting bilirubin In testing the blood serum by the direct reaction the characteristic color develops promptly reaching the maximum intensity within 30 seconds and if it should require up to two minutes the result is described as positive direct If the color does not develop within this time but is demonstrable within ten minutes the result is reported as positive in – minutes (delayed direct) The delayed direct reaction has the same significance as a negative direct (in direct) *In the so-called biphasic reaction the* color appears at once but the attainment of maximum intensity is gradual and follows a variable period of delay It is due to the simultaneous presence of bound (indirect reacting) and free (direct reacting) bilirubin in the serum and indicates both some degree of obstruction of bile canali culi and parenchymal liver damage

The accepted practice with the qualitative van den Bergh test is to report the direct reaction as positive or negative the biphasic reaction is termed merely a positive direct while both the com pletely negative direct and the delayed direct reactions are reported as negative direct

The *small amount of bilirubin present* in the blood in health gives the indirect reaction (negative direct) It is also indirect in hemolytic jaundice A direct van den Bergh in the presence of hemo lytic icterus indicates an associated hepatic or biliary disorder A direct reaction even in the absence of any other evidence of liver damage is always a pathological finding implying a disturbance in the excretion of bile pigment From a clinical standpoint little attention need be given to biphasic or delayed direct reactions

The intensity of bilirubinemia may be described as mild (values up *to 10 mg per cent) moderate (10 to 20 mg* per cent) and severe (above 20 mg per cent) It is important to repeat estimations of the degree of bilirubinemia at short intervals so that not only the intensity of jaundice but also the constancy of its level or its tendency to fluctuate can be ascertained

In health the value for bilirubin does not ordinarily rise above 0 6 mg to 0 8 mg per 100 cc of serum In obstructive jaundice resulting from a common duct stone *the average value for the serum* bilirubin is 10 to 15 mg per cent fluctuations frequently are ob *served and there is a* general tendency for bilirubinemia to de crease In obstruction of the common bile duct by a malignant

The methylene blue test has been recently introduced It is quite simple and is performed by adding 0 25 per cent aqueous solution of methylene blue chloride to 5 cc of urine drop by drop, employing a medicine dropper delivering about 20 drops per cubic centimeter If a green color develops and persists after the addition of 3 drops, but turns to blue after 4 drops, the test is recorded as mildly positive If the green persists after 4 drops or more it is definitely positive This may be a sensitive test for bilirubin, although the mechanism of the reaction is not entirely clear Its use in a recent outbreak of infectious (epidemic) hepatitis gave results that indicated its possible value in the early diagnosis of the disease The validity of the test remains in question because other urinary pigments may interfere

A relatively simple test for bilirubin in the urine, described in 1937 by Harrison has been recently modified with still further simplification by Hawkinson and Watson The technique is as follows pieces of extra thick and retentive filter paper (Schleicher and Schull number 470) are allowed to remain briefly in a saturated aqueous solution of barium chloride After drying, they are cut into strips about 4 inches long by ½ inch wide A single strip is used for one test One end of the strip is placed in the urine sample to be tested, where it remains for from thirty seconds up to two minutes Two to three drops of Fouchet's reagent (25 per cent of trichloroacetic acid containing 0 9 per cent ferric chloride) are then dropped on the area of the strip corresponding to the surface of the urine, this area being indicated by somewhat more color A positive test is denoted by the appearance of a green color, varying in intensity with the amount of bilirubin present This procedure is easily applicable to mass usage, for screening purposes, and is more accurate and dependable than the methylene blue test, described above.

Determinations of Urobilinogen in the Urine and Feces

The discussion of laboratory tests employed in the differential diagnosis of jaundice can hardly be complete without the inclusion of examination of urine and feces for the presence or absence of urobilin Normally, urobilinogen is not present in urine and stool, or it can be found only in traces in a fresh specimen, as on standing it becomes oxidized and converted into urobilin

van den Bergh is an aid in studying not only the daily fluctuations in intensity of jaundice but also in detecting latent icterus

Although the extent of biliary obstruction chiefly determines the intensity of jaundice in the presence of complete obstruction there are two additional factors that play a role in determining the degree of bilirubinemia The most important of these is the rate and manner of hemoglobin wastage It has been established that the loss of blood in experimental animals with complete biliary occlusion is followed by a decrease in the intensity of icterus This probably results from a compensatory slowing down of the rate of physiological blood destruction Similar instances of the effect of blood loss on the degree of jaundice have also been observed in clinical practice Conversely in some cases of parenchymatous jaundice associated with an increased rate of hemolysis the icterus index is very high in spite of the fact that considerable bile is obviously entering the intestinal tract Excessive blood destruction may be caused by infection and other pathological processes initially responsible for or accompanying liver injury Hemolysis may explain why in hepatitis the stools may continue to have a normal or nearly normal color in spite of mounting jaundice

Determinations of Bilirubin in the Urine

The standard methods for the detection of bilirubin in the urine are the foam test the time honored nitric acid contact test of Gmelin and the iodine ring test The first mentioned procedure is very simple shake urine in jaundice the foam will be stained with bile The iodine test is also very simple the surface of a urine specimen is stratified by a layer of alcoholic iodine solution prepared by diluting tincture of iodine 1 to 10 with 95 per cent alcohol the result is positive when a green ring forms at contact The Sparkman modification of Gmelin test is as follows to a small amount of freshly voided urine in a flask add anhydrous calcium chloride in a proportion of 50 cc of urine to 2 gm of the salt Mix the combination well and filter The residue on the filter is used in the detection of bile pigment Pour a few drops of concentrated nitric acid down the side of the filter In the presence of bilirubin a colored zone is produced that consists of a central area of pink (choletelin) and a periphery of green (biliverdin) As much as five minutes may be necessary for full development of the color

ferentiate between these conditions in two thirds of the cases In the remaining cases it is impossible to arrive at a satisfactory solution on the basis of the above mentioned methods of investigation and additional studies must be made These include observations on bile pigment metabolism (quantitative determinations of urobilin in urine and stool) and certain liver function tests Such tests aid materially in differentiation between hepatitis benign obstruction and malignant obstruction Watson has worked out a very reliable method for the quantitative determination of urobilin in urine and feces and has demonstrated it to be of a definite clinical value It represents a modification of the original Terwen s procedure Unfortunately the method is too elaborate for an ordinary laboratory It is applied to one or more 24 hour urine specimens and to one or more 4 day collections of stool According to Watson it is essential that the 4 day collection include at least 250 gm of relatively solid feces If it is necessary to use enemas the liquid and solid portions are separated and a determination is carried out on each provided the solid portion weighs at least 250 gm If less than this amount is present in the collected specimen it is believed either that some has been lost or that constipation has been so marked as to prevent any accurate conclusions In the presence of diarrhea determinations are of value with respect only to biliary obstruction not to the rate of blood destruction The values are expressed in terms of milligrams of urobilin excreted in urine or feces in a 24 hour period Sparkman s method is more rapid and much simpler The determinations are carried out on individual samples of feces and urine and the values are expressed in terms of milligrams per hundred grams or hundred cubic centimeters respectively They yield results that check with those of Watson s for all practical purposes Watson has published recently (1944) a simplified technique for quantitative estimation of urobilin obviating the more elaborate and exact petroleum ether extraction of the original procedure The method is not specific for urobilin and includes other Ehrlich reacting substances However as the increase in the latter is roughly proportional to that of urobilin Watson feels that from a clinical standpoint the information gained compares favorably with that obtained by the exact quantitative analysis The simplification of the procedure permits a large num

The significance of urinary and fecal urobilin has already been discussed briefly The substance can be determined both qualitatively and quantitatively In normal urine urobilin will be found only in concentrated dilutions

Qualitative Determinations In the aldehyde test Ehrlich s reagent is used for the qualitative urobilin estimation in the urine The test is very simple The reagent is prepared by dissolving 2 gm of pure para dimethyl amino benzaldehyde in 100 cc of 20 per cent hydrochloric acid solution *1 cc of the reagent is added to a speci*men of urine A deep red color will appear in three minutes if urobilin is present Watson feels that this test is not carried out *properly in that too much Ehrlich* s reagent is employed and sodium acetate is not used The latter has the advantage of intensifying color produced by urobilinogen and making the color due to indole and skatole fade thus eliminating false positives The modified reagent he recommends is as follows

0 2 gm of pure para dimethyl-amino-benzaldehyde
150 cc of concentrated (37%) hydrochloric acid
100 cc of distilled water

The reagent with sodium acetate is added to 5 cc of freshly voided urine cooled at room temperature

It should be remembered that there are certain limitations to all qualitative determinations of urobilin the degree of dilution or concentration of urine and feces has to be considered in the interpretation of results

Quantitative Determinations Whereas on the basis of a good history and a careful physical examination it may be possible to make a presumptive diagnosis in about 50 per cent of the cases the percentage may be raised to about 70 by qualitative analysis of urine for bilirubin and urobilin These determinations should show which patients have the retention type of jaundice as in that group of cases there is an increase in urinary *urobilin in the absence of* bilirubin Thus clinical examination with qualitative tests on the urine will *eliminate hemolytic icterus* The question will then remain whether the patient has parenchymal liver disease or obstruction In the latter instance a decision has to be made regarding the nature of the obstructive *lesion is it benign or malignant?* History physical examination and urinanalysis may suffice to dif

ferentiate between these conditions in two thirds of the case the remaining cases it is impossible to arrive at a satisfactory tion on the basis of the above mentioned methods of investig: and additional studies must be made These include observatio bile pigment metabolism (quantitative determinations of urobi' urine and stool) and certain liver function tests Such tests ar terially in differentiation between hepatitis benign obstruction malignant obstruction Watson has worked out a very re method for the quantitative determination of urobilin in urin feces and has demonstrated it to be of a definite clinical val represents a modification of the original Terwen s procedure fortunately the method is too elaborate for an ordinary labor: It is applied to one or more 24 hour urine specimens and t or more 4-day collections of stool According to Watson it is tial that the 4-day collection include at least 250 gm of rela solid feces If it is necessary to use enemas the liquid and portions are separated and a determination is carried out on provided the solid portion weighs at least 250 gm If less tha amount is present in the collected specimen it is believed that some has been lost or that constipation has been so m as to prevent any accurate conclusions In the presence of rhea determinations are of value with respect only to biliar struction not to the rate of blood destruction The values a pressed in terms of milligrams of urobilin excreted in uri feces in a 24 hour period Sparkman s method is more rapi much simpler The determinations are carried out on indiv samples of feces and urine and the values are expressed in of milligrams per hundred grams or hundred cubic centin respectively They yield results that check with those of Wa for all practical purposes Watson has published recently (a simplified technique for quantitative estimation of urobilin ating the more elaborate and exact petroleum ether extracti the original procedure The method is not specific for urobili includes other Ehrlich reacting substances However as th crease in the latter is roughly proportional to that of urobilin son feels that from a clinical standpoint the information g compares favorably with that obtained by the exact quanti analysis The simplification of the procedure permits a large

ber of determinations and frequent serial examinations in individ ual cases

In any case of clinical jaundice of moderate or severe degree there is usually sufficient liver damage present to cause pathologic urobilinuria However if the bile passages are completely occluded there will be no increase in urinary urobilin since bile fails to reach the intestine Thus in the obviously jaundiced patient the determinations of fecal and urinary urobilin are more helpful in the differential diagnosis of jaundice than in the detection of impair ment of liver function Parenchymatous jaundice is usually asso ciated with an increase in urinary urobilin In the presence of com plete occlusion of the extrahepatic biliary system as is usually the case with neoplastic obstruction urobilin disappears from both the *stool and the urine In partial obstruction as by a common duct* stone fecal urobilin is decreased but rarely completely absent Uri nary urobilin is then also decreased However if the obstruction is slight and the hepatic damage is considerable there may be an *increase in urinary urobilin as the damaged liver is unable to re* move from the blood this derivative of bile pigment absorbed back into the circulation from the intestinal tract As a result a con siderable amount of it is left for excretion by the kidneys In paren *chymatous jaundice (hepatitis) there is at first a rise in the level* of urinary urobilin into the pathologic range At the height of the disease as complete intrahepatic obstruction develops it disappears from both the stool and urine very much as in the case of malignant obstruction or transient complete occlusion by a stone However with a stone in the common duct the obstructive stage usually lasts only a few days at a time During this period the icterus index and the serum concentration of bilirubin attain their highest level With spontaneous relief of intrahepatic or benign extrahepatic obstruc tion urobilin reappears in the stool At the same time it also re appears in the urine in greatly increased amounts not only in parenchymatous jaundice but in benign obstruction as well when ever the latter is associated with secondary liver damage As hepati tis subsides urobilin in the urine begins to diminish slowly

From the point of view of differential diagnosis the findings above set certain limitations on the range of usefulness of the labo- ratory procedure under discussion Thus in one and the same group of conditions as in hepatocellular jaundice urobilinuria may be

present or absent, depending upon the stage and severity of the disease * Moreover, urobilinuria characterizing parenchymal liver involvement may also be observed in incomplete extrahepatic obstruction complicated by secondary liver damage Obviously, single estimations do not have the same value as a series of determinations. With only one determination the results may be the same in the different types of jaundice, whereas repetition of the test over a comparatively short period (several days or a week) may aid in the differential diagnosis For example urobilin will be absent from the urine only for a few days in hepatogenous icterus (during intrahepatic obstruction) but permanently in malignant occlusion of the common bile duct

The fact that urobilinogen may be formed in tissues other than the intestine and thus be excreted in excessive amounts under certain conditions (splenic and pulmonary infarction and hematomas in various locations) also would tend to limit the value of these tests However, there is no convincing evidence that urobilinogen is formed outside of the intestinal tract

In spite of all drawbacks certain useful generalizations can be made with regard to proper evaluation of the results of quantitative urobilin estimation

The presence of urobilinogen in the urine at once rules out the possibility of complete obstruction except in very rare instances of superimposed cholangitis where bacterial action in the bile ducts converts bilirubin to urobilinogen The condition may be that of parenchymatous jaundice or a stone in the common duct Quantitative determinations of urobilinogen in urine and stool will show which of the two is the offending lesion In parenchymatous jaundice urobilinogen usually rises to a high level in the urine, while in the feces its content is comparatively low These values in the urine remain at a relatively even level for the duration of the disease In the case of a common duct stone (or early and incomplete malignant obstruction) the urinary urobilinogen values are usually only moderately increased while in the stool they may remain within the normal range The amounts of urobilinogen usually

* In hepatitis urobilin may be absent from the urine not only during the stage of intrahepatic obstruction when little or no bile is entering the intestine but also in the presence of diarrhea due to the rapid movement of intestinal contents through the colon leaving little time for reduction of bilirubin to urobilinogen or reabsorption of urobilinogen into the circulation Also, renal insufficiency may interfere with the appearance of urobilin in the urine

fluctuate from day to day It is in these patients that liver function tests are of value as additional diagnostic aids

The absence of urobilinogen from the urine points to complete obstruction whether it be intra or extrahepatic in origin Continuous absence of urinary urobilinogen (daily urobilinogen of less than 0 5 mg) along with the stool values for urobilinogen below 5 mg per day is usually found only in malignant obstruction In intrahepatic obstruction of parenchymatous jaundice small quantities of urobilinogen (1 or more mg in the urine and above 10 mg in the stool) may appear intermittently In rare cases of complete obstruction by a stone impacted in the common duct urobilinogen excretion is not as persistently low as in malignant obstruction and is somewhat variable being usually above 1 mg The quantitative determination of excreted urobilinogen is particularly important in cases of obstructive jaundice as such small amounts can rarely be determined qualitatively especially in the presence of bilirubinuria

In patients with complete obstruction resulting from malignancy urobilinogen is absent from the urine even in the presence of secondary liver damage because no bile enters the duodenum A temporary relief of obstruction may occur in rare cases of carcinoma of the ampulla of Vater when part of the necrotic tissue sloughs off periodically permitting the escape of bile thus leading to the appearance of small amounts of urobilinogen in the stool and feces In such cases occult blood will also probably be found in the stool or in duodenal drainage

In malignant disease incomplete biliary obstruction is encountered in less than 10 per cent of cases In addition to temporary relief of obstruction by slough of necrotic tumor tissue this group includes minute carcinomas of the ampulla of Vater or common duct and polypoid tumors Reference has already been made to the fact that the intensity of jaundice is not determined solely by the obstructive factor Decreased bilirubin formation or diminution in the rate of blood destruction following blood loss results in a decrease of icterus even though the biliary obstruction may remain complete Occasionally in the continued absence of urobilinogen from urine and feces in patients with malignant obstruction clinical jaundice may paradoxically enough become lighter and the icterus index may drop slightly This may be due to (1) progressive anemia usually occurring in patients with malignancy (2) variation in the

rate of destruction of red blood cells and (3) decreased erythrocyte fragility which seems to occur in these conditions On the other hand sudden increase in the intensity of jaundice in these patients may be caused by some superimposed toxic factor or secondary extensive liver damage In some cases of parenchymatous jaundice urobilinogen is found in markedly increased amounts in the urine while the stool content of urobilinogen is very low This may be

	I I	F U	U U	I I	F U	U U	I I	F U	U U
400					4			4	
200				2	9		1	7	2
100	28			5	15	1	16	11	4
50	19			25	11	2	24	15	8
20	4	2	1	29	15	8	20	10	8
10		1		6	6	17	1	6	13
5		1	1		2	7		5	7
1		20			5	16		2	12
0 3		29	3		2	4			2
	I			II			III		

F
f
s
a
56 per cent Group III parenchymal jaund ce 57 cases autopsy in 19 per cent From C. J Watson Courtesy of *J A M A*

due to associated biliary tract infection or to severe impairment of liver function with regard to the ability of converting urobilin ogen back into bilirubin The latter possibility would make the disparity between the quantity of urinary and fecal urobilinogen an important diagnostic factor of liver damage

Urobilinogen is found in the feces in large amounts in hemo lytic jaundice and quite out of proportion to the amounts in the urine although in the urine it may also be significantly increased The same finding is observed in hemolytic septicemias and in some cases of hepatitis associated with increased hemolysis Fecal uro bilinogen is commonly higher in hemolytic jaundice with marked

anemia or during hemolytic crisis although there is no strict correlation *Cases of hemolytic icterus* are encountered with marked increase in fecal urobilinogen but with a normal amount in the urine as long as the liver function remains undisturbed Such patients may have marked anemia but relatively little or even no jaundice In general *it may be stated that the more anemia the* less jaundice and urobilinuria and vice versa However the immediate period of hemolytic crises constitutes an exception to this

The extensive investigations of Watson furnish the most complete and exact information regarding the excretion of urinary and fecal urobilinogen in health and disease However from a practical point of view there is an objection to his method of urobilinogen determination on the feces because 4 day specimens of stool often cannot be obtained owing to illness and limited diet

The urobilinogen content of the stool in health varies widely from day to day The normal range is 40 to 280 mg in 24 hours usually 100 to 200 mg Urinary urobilinogen varies within much narrower limits the range being between 0 and 4 mg a day usually 0 5 to 1 5 mg The value for the feces is an average for a 4 day period whereas that for the urine is for 24 hours

Watson gives the following values for fecal and urinary urobilinogen in the different types of jaundice

In hemolytic icterus fecal urobilinogen ranges from 300 to 4000 mg per day usually 600 to 2000 mg while urinary urobilinogen varies from 1 0 to 200 mg per day usually 5 0 to 30 0 mg

In carcinoma of the biliary tract (the main hepatic ducts the *common bile duct or the ampulla of Vater) there is complete* biliary obstruction in 90 per cent of the cases and fecal urobilinogen is less than 5 mg while the urinary urobilinogen is less than 0 5 mg per day

In common duct stone where incomplete biliary obstruction is present in about 90 per cent of the cases the fecal urobilinogen varies from 7 0 to 600 mg and the urinary urobilinogen from 0 to 50 mg per day With rapidly diminishing jaundice following spontaneous relief of obstruction large amounts may be encountered for a short period With low grade obstruction the amount may be within the normal range An impacted stone does not always result in complete occlusion and conversely the stone or stones may be entirely loose in the duct the reason for complete

obstruction not being apparent The amount of urinary urobilinogen will depend on (1) the duration of biliary occlusion, which is the *determining factor in development* of biliary or obstructive cirrhosis, (2) the presence or absence of cholangitis, and (3) the degree of obstruction Small amounts of urinary urobilinogen indicate hepatic functional impairment if but *small* amounts are present in the feces This is true in any case of jaundice, whatever the cause

In postoperative or benign stricture, where, in the majority of instances the obstruction is incomplete but at the same time com

TABLE VI

CLINICAL LABORATORY FINDINGS IN THE THREE MAIN TYPES OF JAUNDICE

		Blood—van den Bergh	*Urine*			*Feces—Urobilin*
			Bilirubin	*Bile Salts*	*Urobilin*	
Hemolytic Icterus		indirect	o	o	+	increased
Parenchymatous Jaundice	Initial Stage	indirect	o +	o	+	normal or decreased
	Stage of Intrahepatic Obstruction	direct	+	+	o	decreased or absent
	3rd Stage of Beginning Recovery	direct	+ o	+ o	+ o	normal
Benign Obstruction (Stone Stricture)		direct	+	+	+	normal or decreased
Malignant Obstruction		direct	+	+	o	absent
Normal		indirect	o	o	o	normal

plete obstruction is encountered more frequently than with a common duct stone, the fecal urobilinogen ranges from 0 to 300 mg, and the urinary urobilinogen from 0 to 50 mg per day

In parenchymatous jaundice, the fecal urobilinogen varies from 0 to 1000 mg per day, usually 10 to 300 mg, and the urinary urobilinogen from 0 to 300 mg, usually 0 5 to 100 mg

Grossly acholic feces may contain from 10 to 15 mg of urobilinogen per day correspondingly, a twenty four hour urine *sample may exhibit a* negative qualitative Ehrlich reaction, and yet by the quantitative method as much as 15 mg per day may be detected During the third or receding stage of acute hepatitis, urobilinogen usually *reappears in the urine in* large amounts Serial quantitative tests are of much value at this point, some may often reveal the first evidence of beginning improvement—that is, the re establishment of bile flow to the intestine. [Watson]

Determination of Bile Salts

The quantitative methods for determinations of bile salts are both very difficult and inadequate and therefore are not important in the differential diagnosis

Tests of Liver Function and Activity of Liver Disease

These procedures are particularly helpful in detecting subclinical or confirming clinically obvious liver damage without jaundice or in the stage of latent icterus Once clinical jaundice has become established, many of these tests are of no value at all, whereas a few still can be used to some advantage in the differential diagnosis

✓ Tests of the Excretory Capacity of the Liver

Bilirubin Excretion Test This test probes the capacity of the liver to excrete into the bile a normal constituent of the blood The injection of bilirubin as a means of testing hepatic function, first introduced in Germany in 1927, was developed in this country by Harrop and Barron The value of this test as a measure of the excretory function of the liver has been well established, and it seems to be a very sensitive determination *It is based on* fairly strong evidence that the injected bilirubin is not stored, but ex

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The relation between the retention of dye in the blood and the histological changes in the liver appears to have been well estab

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Grossly acholic feces may contain from 10 to 15 mg of urobilinogen per day correspondingly a twenty four hour urine sample may exhibit a negative qualitative Ehrlich reaction and yet by the quantitative method as much as 15 mg per day may be detected During the third or receding stage of acute hepatitis urobilinogen usually reappears in the urine in large amounts Serial quantitative tests are of much value at this point some may often reveal the first evidence of beginning improvement—that is the re-establishment of bile flow to the intestine [Watson]

Determination of Bile Salts

The quantitative methods for determinations of bile salts are both very difficult and inadequate and therefore are not important in the differential diagnosis

Tests of Liver Function and Activity of Liver Disease

These procedures are particularly helpful in detecting subclinical or confirming clinically obvious liver damage without jaundice or in the stage of latent icterus Once clinical jaundice has become established many of these tests are of no value at all whereas a few still can be used to some advantage in the differential diagnosis

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lished Its greatest value is in the diagnosis of liver disease in patients without hyperbilirubinemia for *when jaundice is present* the test merely shows the impairment already indicated by retention of bilirubin and thus furnishes no additional information Moreover there is difficulty in determining accurately the degree of retention in highly icteric serum The test does not give reliable results in cases of clinical icterus i e in instances in which the value of serum bilirubin is more than 5 or 6 mg per cent *

It must be remembered that the method of bromsulphthalein test involves two factors the functional status of the liver with regard to dye excretion and the functional integrity of the blood circulatory system for the simple reason that the method includes the measurement of the dye remaining in the blood stream after a given time Thus in congestive failure abnormal retention of the test substance in the circulating blood may well be expected not only on the basis of hepatocellular component but also because of the circulatory factor Therefore the proper evaluation of results in the study of liver disease must take into account the possible factor of deranged circulatory dynamics In other words the performance of the test in patients with hepatic disease occurring in the presence of coexistent cardiovascular abnormalities requires a simultaneous appraisal of the latter (by means of the determination of the circulation time) with a view either to ascertain possible circulatory factors in the retention of the dye or to establish the essentially hepatic nature of the dysfunction

Rose Bengal Test This is another dye test that yields results similar to those with bromsulphthalein *It has the same limitations* in its application to jaundiced cases particularly in the obstructive type Generally speaking in biliary obstruction the retention of the dye *will be observed in the presence* or absence of liver damage However the test can be carried out in the presence of jaundice or/and moderate hemolysis A spectroscopic method has been applied *to the determination* of rose bengal Ten cc of a 1 per cent solution of the dye in triple distilled water are injected intravenously At 2 minutes 8 minutes and 16 minutes after the injection 5 cc of blood are collected from a vein in the other arm Rose bengal is estimated in the sample by spectroscopic method A

* However with the photoelectric method determinations can be made accurately on icteric serums

normally functioning liver will remove 50 to 55 per cent of the dye present at 2 minutes and 30 to 35 per cent at the end of 16 minutes Photosensitization and the preciseness of time intervals limit its use clinically

Azorubin-S Test This procedure tests the capacity of the liver cells to excrete a foreign dye into the bile This is a dark red water soluble substance that is nontoxic in the doses employed for diag nostic procedures It is excreted by the liver to the extent of 95 per cent A dose of 4 cc of a 1 per cent solution is injected intra venously and 5 minutes later 40 cc of a 25 per cent solution of magnesium sulphate is administered through a duodenal tube Sam ples of duodenal contents are then collected at 2 minute intervals In health the dye appears with deep cherry red color in 15 to 30 minutes Its appearance is delayed in diseases of the liver It is one of the few dye methods that directly test the excretory function of the liver since it requires recovery of the dye from the duodenum rather than its disappearance from the blood as in the case of rose bengal or bromsulphthalein The method also lends itself to a simul taneous crystallographic study of the bile

The test of course will give a negative result in the presence of complete common-duct obstruction and variable results in both liver disease and incomplete biliary occlusion depending upon the degree of functional impairment of the liver and the patency of interhepatic and extrahepatic biliary passages It can hardly be re garded as a procedure for differential diagnosis of jaundice although it is a valuable test of liver function comparing favorably with the bromsulphthalein test

Serum Phosphatase Test Serum phosphatase (alkaline) is an en zyme that hydrolizes phosphoric acid esters liberating the phosphate ion The liver may be an important source of this enzyme Altera tions in the activity of the serum phosphatase have been found in diseases of the liver and bone Coexistent osseous disease must therefore be excluded whenever the test is undertaken for the study of jaundice

In hemolytic icterus the plasma phosphatase is normal or shows no significant increase while in parenchymatous jaundice it may be either normal or slightly increased The most marked elevation of serum phosphatase appears to occur most frequently in extrahepatic obstruction Unfortunately rather a wide range is observed in both

liver disease and gross obstruction so that there is sufficient over lapping to make the test of doubtful usefulness in differentiating between the two However, some workers feel that readings are significantly higher in obstructive jaundice than in hepatitis They maintain that the test is of definite value as a supplementary aid to the clinical differentiation between several types of jaundice, and of particular value in ruling out obstruction of the extrahepatic biliary tract, an improbable cause of jaundice in patients with serum ✓phosphatase less than 10 Bodanksy units per 100 cc In hepatitis al though the serum phosphatase may be elevated, in most instances the level of 10 units per cent is not reached (normal is 2 to 4 units) although in some cases of liver damage (toxic hepatitis) higher readings than 10 units per 100 cc may be encountered The increase of the phosphatase level in jaundice is probably not en tirely related to the obstructive factor

Tests of Metabolic and Detoxifying Functions of the Liver

Tests of Carbohydrate Metabolism

Galactose Tolerance Test The use of galactose for testing liver function was introduced in 1906 It is one of the sugar tolerance tests employed to determine deviations from the normal in the hepatic function concerned with the metabolism of carbohydrates It is based on the fact that galactose is metabolized exclusively by the liver and independently of insulin This sugar is converted in the liver into glycogen with greater difficulty than other carbohy drates and therefore is considered to be better suited for diagnostic purposes It is thought to be superior to levulose or glucose tolerance tests because organs other than the liver play an important role in their metabolism and because there is no renal threshold for galactose In the performance of the test this carbohydrate may be administered orally or intravenously, and either the blood or the urine tested after an interval for its content of galactose When the sugar is administered intravenously, the test is spoken of as the 'galactose clearance test' It is necessary that the presence or absence of diabetes mellitus be known If the patient is also a diabetic, the sugars must be separated in the urine by differential fermentation

In the method of oral administration and urine testing the patient receives in a fasting state 40 gm of galactose in 500 or 1000 cc of water This amount is slightly above what the normal person can metabolize The urine is collected at intervals of 30 minutes for 4 hours Normally less than 3 gm of sugar is recovered in the urine If sugar is recovered in greater amounts the result is interpreted as indicative of liver dysfunction or at least of impairment of function of that particular phase of carbohydrate metabolism It should be recalled that in the presence of renal insufficiency a false negative test may be obtained

Some investigators believe that the test is of more value in the visibly jaundiced patients than in the absence of icterus It is thought to be helpful in the differential diagnosis of early obstructive jaundice and parenchymal liver disease In early extrahepatic obstruction the test is negative for secondary hepatic damage of significant degree has not had time to develop In acute hepatitis positive results may be obtained early—less than two weeks The duration of jaundice is an important factor in the appraisal of results as the test is of questionable differential value after icterus has persisted for several weeks a period sufficient to allow for secondary liver damage The procedure has been found to yield positive results in 32 to 46 per cent of patients with surgical obstructive jaundice in whom the obstruction has persisted for a sufficient length of time to injure the hepatic parenchyma In another series of cases positive reactions were obtained in 50 per cent of patients with intrahepatic disease while only one positive test was found in the 12 suffering from obstructive jaundice In obstructive cases the test may become positive at the end of 2 weeks Thus while the results may be mildly positive in as much as 50 per cent of cases of malignant obstruction and in about 25 per cent of cases of obstruction due to stone or cicatricial structure normal values may at times be obtained in parenchymatous jaundice However it appears that the test generally speaking is more frequently positive in hepatocellular jaundice than in cases of extrahepatic obstruction Thus it possesses some limited value in the differential diagnosis One should constantly keep in mind the fact that severe hepatitis (or inflammation of the ducts) secondary to extrahepatic obstruction will give a positive test and may cause one to overlook mechanical blockage of the common bile duct A borderline positive test i e the excretion

of 3 or 4 gm is not to be considered as conclusive evidence that a mechanical obstruction is not present

Because of variable and uncertain absorption from the intestine and the dependence of *excretion of excess sugar on the renal* state of efficiency there is some question of the reliability of the oral test To obviate this uncertainty an intravenous galactose test has been devised One cc of 50 per cent galactose solution per Kg of body weight is injected intravenously over a period of 5 minutes and the blood is tested 75 minutes later In this period normal persons clear the blood completely while patients with hepatitis retain an average of 45 mg per 100 cc and those with obstruction 14 mg per 100 cc It is possible that this test is more sensitive than the oral one Thus in one series of cases reported 81 per cent of patients with liver disease manifested a plasma retention of more than 20 mg per cent of galactose while 82 *per cent of patients with mechanical* obstruc tive jaundice of shorter duration than 6 months showed retention of less than 20 mg per cent The technique of the intravenous test is more involved than that of the oral one requiring three venipunc tures *As in the oral test the differential* value of the procedure is reduced in cases of obstructive jaundice of long duration

Glucose Tolerance Test The role of the liver in carbohydrate metabolism has been discussed in the chapter on physiology That there may be hypoglycemia in severe liver damage is well estab lished While galactose is now usually employed for testing the gly cogenic function of the liver this test may occasionally be found to be normal when the glucose tolerance test gives abnormal values At times a fairly characteristic curve is found in liver disease a normal or low fasting blood sugar a rise above normal in the first and second hours and a fall to hypoglycemic levels during the third fourth and fifth hours There is some evidence to the effect that both hyper and hypoglycemia may under certain circumstances have their origin in a disturbed glycogenic function of the liver Striking differences in results in various types of jaundice have been reported *The dependence of the glucose* tolerance curve on a multi plicity of factors (pituitary adrenal thyroid pancreas fat and carbo hydrate content of the diet etc) make this test of very limited value and deprive it of any specific diagnostic significance

Hippuric Acid Synthesis Test The use of sodium benzoate as a means of testing liver function was introduced in 1932 It involves

a process of detoxification of benzoic acid used as a test substance by conjugation with glycine which is synthesized in the liver The hippuric acid thus produced in the liver is determined quantitatively in the urine Since the body does not store glycine the amount of hippuric acid that is recovered tests not only the capacity of the liver to conjugate benzoic acid with glycine but also the power of the liver to synthesize glycine The maximum amount of hippuric acid that can be synthesized by the liver is limited practically constant and independent of the exact amount of sodium benzoate ingested—provided the test dose of benzoic acid given is in excess of the liver s capacity to conjugate it all with glycine within a fixed period of time

The capacity to form hippuric acid from benzoic acid is limited by the available glycine In health about 1 5 gm is the maximum amount of sodium benzoate the liver can convert into hippuric acid per hour Peak production is obtained by a dose of 4 gm of sodium benzoate and cannot be raised by increasing this dose The simultaneous administration of glycine may materially increase the amount of hippuric acid formed and excreted A decrease in the amount of hippuric acid excreted after giving benzoic acid may represent either reduced synthesis of glycine or reduced conjugation of benzoic acid These two functions of the liver may be distinguished The amount of hippuric acid eliminated in the urine may be estimated gravimetrically The use of the hippuric acid test is invalid in the presence of renal insufficiency for then the renal excretion of hippuric acid would be slower than the rate of its production thus giving a false positive result Since the excretion may be diminished in renal disease the value of the test for liver function may be enhanced by a determination of the rate of renal excretion of hippuric acid which normally averages about 3 5 gm per hour

Benzoic acid is administered orally as sodium benzoate in the dose of 4 to 6 gm The standard result for normal individuals is the recovery of 3 to 3 5 gm of the test substance as hippuric acid in the urine in 4 hours after its ingestion The oral dose of 4 gm is more satisfactory because while being sufficient to tax the capacity of the liver fully it is less likely to cause vomiting than the 6 gm dose

The intravenous test is quite commonly employed and consists in the administration of 1 5 gm benzoic acid in the form of sodium

benzoate (1 77 gm) injected into the vein in 20 cc of sterile water In healthy individuals about 50 per cent (0 7 to 0 95 gm) is re covered in the urine as hippuric acid in 1 hour

The procedure is applicable to both jaundiced and non jaundiced patients Severe hepatic damage may be assumed if on oral test the 4 hour hippuric acid elimination is reduced to 1 5 gm or less or with the intravenous test to 0 7 gm or less in 1 hour The intra *venous test is more sensitive than the oral one and yields 85* per cent more positive results in identical cases It tests the maximum amount of work the liver can perform in a comparatively short period whereas the oral test allows 4 hours for the slightly im paired liver to catch up with the amount of work a normal organ can probably perform in a considerably shorter time Also the uncertainty of intestinal absorption is eliminated the intravenous administration insures accurate dosage and *requires a smaller* amount of benzoic acid Moreover the patient may not be in the position to ingest and retain the test substance

At times the amount of hippuric acid excreted may be consid erably in excess of the amount of the test dose administered (117 to 166 per cent of normal) The significance of this finding is not clear The apparent excessive excretion of hippuric acid may be due to the excretion of sodium benzoate itself which contaminates the pre cipitate and thus simulates a falsely high level Or it may signify a manifestation of *hyper irritability of the liver in early hepatic* damage

Although it is a fairly sensitive test of liver function there has *been considerable difference of opinion about its value as a diag* nostic aid in the differential diagnosis of icterus It may not help materially in distinguishing obstructive from hepatocellular jaun dice particularly when the former condition has been present for two weeks or longer In Moser s series less than 0 7 gm of hippuric acid was excreted in the following conditions acute hepatitis portal cirrhosis extensive metastases to the liver post cholecystectomy with associated hepatitis and late pregnancy between 0 7 and 1 0 gm was excreted in post cholecystectomy cases acute cholecystitis sub siding acute hepatitis and congestive heart failure (with urea clearance of 43 per cent factor of renal insufficiency or pre renal azotemia)

In the absence of impaired renal function the intravenous hippuric acid test can be used to evaluate the extent of hepatic insufficiency

Amino Acid Tolerance Test In experimental animals with damaged livers there is a retention of plasma amino acids after the intravenous injection of casein hydrolysate This appears to represent a delay in the hepatic function of deamination In children with cirrhosis of the liver similar plasma retention of injected amino acids has been observed Such retention does not occur in severe kidney disease with impaired renal function for deamination proceeds in a normal fashion In patients with liver disease there is delay in clearing the plasma of amino acids and there is failure of the normal increase in urinary urea and ammonia excretion following the injection of these acids since urea and ammonia represent normal products of deamination of amino acids by the liver The injection of amino acids therefore seems to provide a method for evaluating the deaminizing capacity of the liver Spontaneous hyperamino acidemia is an extremely rare but important manifestation of serious liver damage and is observed only on rare occasions

A related topic is the presence of leucine and tyrosine crystals in the urine of patients The clinical incidence of tyrosinuria was analyzed in one series of 76 patients with jaundice It was demonstrable in approximately a third of the 76 cases and the incidence was highest in acute and subacute liver necrosis (67 per cent) It is important to note that it was also found in approximately 25 per cent of cases of common duct stone and infections of the biliary tract and therefore cannot be used as an absolute criterion in the differential diagnosis of jaundice Approximately 30 per cent of patients with neoplastic disease of the liver gall bladder and bile passages also present this finding Tyrosinuria is far from being of constant occurrence even in the presence of subacute liver necrosis and hepatic coma If marked however it is a valuable sign of liver damage It is characterized by the following features of pathologic and clinical significance (1) continuous massive tyrosinuria occurs in acute diffuse liver necrosis (2) intermittent tyrosinuria corresponds to cycles of liver necrosis (3) jaundice may prove fatal despite the absence of tyrosinuria and recovery may take place in patients who exhibit intermittent minimal to moderate tyrosinuria However the demonstration of massive tyrosinuria in even a casual speci

men is very strong evidence in favor of a diagnosis of acute liver atrophy In no other circumstances does disintegration of liver tissue proceed at a rate which permits the excretion of such massive amounts of this single amino-acid This finding implies diffuse and continuous autolysis of liver tissue'

Tyrosinuria may appear in the absence of a fundamental disturbance of amino acid metabolism in the liver and therefore may be of twofold origin (1) failure of deamination by the liver, (2) as a result of autolysis of liver tissue

The morphology of authentic tyrosine crystals and leucine bodies is variable The crystallographic method of demonstrating tyrosine in the urine is difficult of performance To obviate false positive results a tyrosinate method for the demonstration of tyrosine crystals in the urine has been devised This method has increased not only the accuracy of the finding but also the frequency of its demonstration In addition, a quantitative estimation has been thus made possible

Plasma Cholesterol Partition Cholesterol occurs in the plasma in *the free form as a sterol and combined with fatty acid as ester* Free cholesterol is a normal constituent of bile There is evidence indicating that the liver possesses the power of removing cholesterol from the blood and storing it, and that esterification of cholesterol with fatty acids is accomplished in the liver Thus the liver appears to have an important influence on the control of the blood cholesterol concentration as well as on the proportion of the free to the esterified form However the level of cholesterol in the blood is also known to be definitely influenced by thyroid activity among other factors (it is low in thyrotoxicosis and elevated in hypothyroidism)

A disturbed cholesterol picture has been found to parallel other functional disturbances in the liver, as, for instance, in obstructive jaundice where the total cholesterol may be elevated Under these *circumstances hypercholesterolemia appears to result in an increase* in the free cholesterol without a concommitant rise in the ester fraction According to some reports however, the increase is the result of increments in both fractions *Some claim that hypercholesterolemia* parallels the degree of hyperbilirubinemia while others dispute such relationship This divergence of opinion may be due to a

number of factors, such as attempts to compare results of analysis of whole blood, serum and plasma use of different technical procedures, failure to realize the wide range, which renders interpretation difficult, of normal concentration of total cholesterol, failure to recognize the narrow range of variation of the normal ratio of free cholesterol to total and failure to recognize the nonspecific

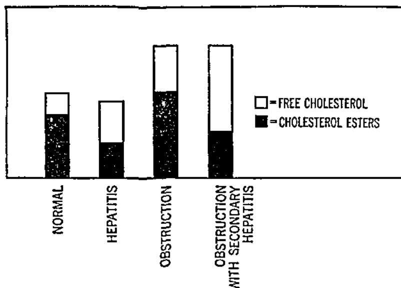


FIG 12 Schematic drawing showing the relation between free and esterified cholesterol in normal persons and patients with liver disease From F Steigmann H Popper and K A Meyer Courtesy of *J A M A*

contribution of various physiologic and pathologic factors to the effect on the plasma cholesterol level

The total plasma cholesterol remains normal or diminished in acute hepatitis At the same time, the ratio of ester fraction to total cholesterol is reduced, at times markedly The ester cholesterol may practically disappear from the blood in severe liver damage. This is understandable as long as esterification is assumed to take place in the liver Cholesterol esters disappear from autolyzed liver tissue, implying inhibition of cholesterol esterase (responsible for esterification) by the products of autolysis and necrosis A persistently low ester cholesterol level has serious prognostic significance, whereas a rising ester level parallels clinical improvement In obstructive

jaundice of long duration with secondary cholangitis and biliary cirrhosis the cholesterol content of the plasma may not rise above normal for hepatic dysfunction has an effect on blood cholesterol in the opposite direction to that exerted by conditions in uncomplicated obstructive jaundice

Hypocholesterolemia found in some patients with hepatic disease is often accompanied by marked anemia a febrile course and failing nutrition Thus great care must be exercised in ascribing to the liver the sole role in influencing blood cholesterol level in disease Since factors other than hepatic functional disturbance may influence the total cholesterol and the ester fraction it is unwise to regard the cholesterol partition necessarily as a liver function test The wide range in variation of the total cholesterol concentration of the blood in health and disease (thyrotoxicosis myxedema nephrosis etc) limits the usefulness of this test in differential diagnosis Moreover the free-cholesterol level may be elevated in both obstructive and hepatocellular jaundice Except for instances in which the ester fraction is definitely depressed or present merely in traces indicating severe liver damage isolated determinations have little value but serial readings may be helpful the trend of values especially in relation to bilirubinemia offers some aid in the differential diagnosis The prognosis is extremely grave if free and ester fractions are both constantly depressed as they are in some cases of acute and severe liver damage

The normal total cholesterol varies between 120 and 230 mg per 100 cc of plasma depending on the method employed while the ester partition in health varies between 50 to 70 per cent of the total

The laboratory technique involved in the estimation of free and ester cholesterol requires considerable experience and skill

Plasma Prothrombin Level The prothrombin time should be determined in all cases of jaundice Such a determination has both diagnostic and prognostic significance It also serves as a guide to therapy

Blood clotting depends upon prothrombin which the liver forms from vitamin K Hypoprothrombinemia with elevation of prothrombin time may be due to a deficient intake deficient absorption or deficient utilization of vitamin K Deficiency of intake is seldom a factor in jaundiced patients As vitamin K is fat soluble the pres

ence of bile salts in the intestinal tract is essential for its absorption Therefore in obstructive jaundice the absorption is deficient and hypoprothrombinemia is common Unless proper therapy is instituted to correct this defect troublesome hemorrhage may complicate surgical intervention

Hypoprothrombinemia also occurs in parenchymatous jaundice, for although the vitamin is absorbed the damaged liver is unable to utilize it properly for production of prothrombin In extrahepatic obstruction the defect can be corrected by oral administration of vitamin K with bile salts which insure its absorption Still better is the parenteral administration of 2 mg of menadione which raises the plasma prothrombin 10 per cent or more in 24 hours In severe liver damage vitamin therapy may prove to be of little or no avail This distinction serves as a basis for a liver function test in those cases of jaundice in which hypoprothrombinemia is known to be present The prothrombin time gives an index of hepatic insufficiency and reveals a bleeding tendency When the prothrombin level falls below 30 per cent of normal bleeding is very likely to occur chiefly from mucous membranes at operation or from wounds postoperatively

The failure of prothrombin response to vitamin K therapy when absorption of the vitamin is assured by the use of bile salts can be interpreted to signify an impairment of liver function There is some response to vitamin K if liver damage is not severe Thus the lack of proper response may serve as an index of hepatic functional impairment The value of this finding has been stressed in the differential diagnosis of hepatocellular and obstructive jaundice

If the prothrombin level is initially found to be within a low range (as determined on two successive days with the results on both tests agreeing within 5 per cent) 2 mg of menadione are administered intramuscularly and determinations are made within 24 48 and 72 hours after its administration If there is less than 10 per cent rise in prothrombin concentration intrahepatic disease is more than likely For example a jaundiced patient who fails to respond with a considerable increase in blood prothrombin to intravenous injection of 2 mg of menadione repeated in 24 hours would not be operated upon as icterus would presumably be due to liver disease and not to obstruction In this test as is the case with other laboratory procedures borderline results are difficult to

interpret The differential response to vitamin K is not absolute for patients with severe parenchymatous jaundice have been encountered who showed good response to vitamin K On the other hand there are many cases of obstructive jaundice in which the extrahepatic obstruction is complicated by secondary liver disease and in such instances subnormal response to vitamin K occurs. Patients with obstructive jaundice who develop cholangitis also show a poor response Poor response to vitamin K in a jaundiced patient with a febrile course cannot be considered as of diagnostic value

For the performance of the prothrombin time test it is required that a relatively low prothrombin level be present that the patient be eating reasonably well (often a handicap in a prolonged and serious illness) and that the subject studied be afebrile These considerations limit the decisiveness of the test in the differential diagnosis Moreover the plasma prothrombin is not consistently abnormal in hepatocellular jaundice this also limits the usefulness of the test Only about 50 per cent of patients with parenchymatous icterus exhibit initial hypoprothrombinemia Still another complication is the fact that hypoprothrombinemia of healing intrahepatic disease responds to vitamin K therapy similarly to that of uncomplicated extrahepatic obstruction

There are two different techniques for determination of prothrombin time The two-stage method is more sensitive and gives more reliable prothrombin levels but the technical difficulties of this test preclude its general adoption as a laboratory procedure for clinical diagnosis The one stage technique does not measure the quantity of prothrombin alone since it is the index of several variable factors such as the amount of prothrombin the rate of conversion of prothrombin to thrombin and the reaction of thrombin with fibrinogen to form the blood clot However it is an excellent practical measure for determination of hemorrhagic tendencies Average normal prothrombin time by the one stage method is approximately 20 seconds Prothrombin time over 30 seconds is abnormal

Alterations in Plasma Proteins The function of the liver in regeneration of pla ins was menti the discussion of physiology In di liver certa tive and quali tative changes in proteins proteinemia is known to exist in c hepatic acute hepatitis Th tion aff e album d results in a

reversal of the albumin/globulin ratio At the same time the value for globulin may be increased In advanced chronic hepatic disease albumin/globulin ratios as low as 0 3 have been observed (The protein content of the serum in health is from 6 to 8 gm per 100 cc with the albumin/globulin ratio about 2 1) The decrease in the concentration of albumin is apparently caused by the liver s failure to produce it and is independent of deficient intake absorption or loss (in ascitic fluid) This point of view is supported by the evidence that albumin is less readily formed than globulin and that albumin and not globulin is reduced The hypoalbuminemia produces a lowered colloid osmotic pressure of the blood and is a factor in the formation of ascites and edema which often occur in chronic and acute diseases of the liver Although hypoalbuminemia is frequently encountered in liver disease there are many patients particularly those in whom the condition is of relatively short duration whose values for total protein are normal and rarely even increased because while the albumin fraction is only slightly decreased the globulin is increased appreciably The reason for globulin increase in liver disease is not entirely clear It occurs in many other conditions such as multiple myeloma tuberculosis etc

The changes described above often are not recognized until late in the disease If however the electrophoretic pattern of the plasma proteins is determined the changes may be discovered earlier The increase in globulin occurs primarily in the gamma globulin fraction which may reach 40 per cent of the total protein partition In obstructive jaundice the gamma globulin is less profoundly altered

Flocculation Tests

In liver disease it often becomes possible under certain conditions to obtain a flocculation of plasma proteins This has been known for a long time but the mechanism of the reaction has been established only recently the reaction becomes positive when gamma globulin is increased These tests do not really constitute measurements of hepatic function They are rather sensitive indicators of qualitative changes in the plasma proteins Therefore they may also become positive in other conditions associated with increase in gamma globulin Included among such flocculation tests are the Takata Ara colloidal gold and the cephalin-cholesterol flocculation reactions

Takata Ara Test This laboratory procedure was first described in 1925 as a new colloidal fluid reaction that was originally employed in an attempt to distinguish between lobar and broncho pneumonia The precipitation or flocculation was thought by the originators of this test to be caused by a change in the proteins brought about primarily by an increase of serum globulins Since serum globulin is also increased in liver disease the test was subsequently adopted in this condition The results are most frequently positive in cirrhosis and acute yellow atrophy Whenever there is a marked reversal in albumin/globulin ratio the test may become positive It is not hypoproteinemia *per se* but the increase in the globulin fraction that is responsible for the positive reaction Doubts exist about its specificity While frequently positive in advanced cirrhosis it is frequently negative in the early stage when a positive result would be most valuable It seems that the Takata Ara reaction is not a specific test of liver function and does not actually afford a means of distinguishing between hepatocellular and obstructive jaundice However it gives positive readings in a high percentage of patients with acute and chronic hepatitis and when repeated at intervals may serve as a measure of the progress of the disease

Serial dilutions of the serum are treated in a series of small test tubes with measured volumes of sodium carbonate and mercuric chloride solution The flocculation in each tube is reported as 0 + ++ +++ and ++++ depending on the presence or absence of flocculation and its degree An unequivocally positive reaction is that in which there is ++++ flocculation in two adjoining tubes with at least +++ flocculation in the neighboring tube on each side (for example 003444421 or 00344321)

Colloidal Gold Reaction This test is based on the observation of alteration in the plasma proteins especially in the euglobulin fraction in the presence of hepatic disease Euglobulin has been shown to play an important role in the colloidal gold precipitation The test is frequently positive in liver disease Thus in one series of cases reported it was found to be positive in all patients studied with cirrhosis in 13 out of 14 patients with acute parenchymatous involvement in 19 out of 25 patients with hepatic neoplasm and in 11 patients suffering from miscellaneous types of liver disease In a control series there were negative results obtained in 73 out of 75 patients suffering from extrahepatic disease and in 20 normal

individuals However in 8 out of 20 patients with syphilis positive results were obtained in the absence of other evidence of hepatic dysfunction

The test is rather time-consuming complicated and subject to false positive reactions Therefore it is not particularly suitable for routine clinical use

Cephalin Cholesterol Flocculation Test This test was introduced in 1939 It is based on the fact that the blood sera from patients with active liver damage possess the capacity to flocculate a colloidal suspension of a cephalin cholesterol emulsion whereas the sera of normal control subjects uniformly produce no flocculation The re action in all likelihood depends on a capacity of an altered globulin constituent of serum to become affixed to the colloidal element of the emulsion The mechanism is thus comparable to that involved in the flocculation test for syphilis as described by Eagle The posi tive reactions are graded + ++ +++ or ++++ depending on the amount of precipitation and clearing in the upper portion of the suspension A 4 + reaction indicates a complete precipita tion of the emulsion with no remaining turbidity of the super natant fluid It is best to use a ripened cephalin preparation exposed to the air for weeks as it gives a more stable suspension less spontaneous precipitation and no false positive reactions A stable cephalin cholesterol reagent mixture is now available

In one series reported only one positive result was observed in over 900 normal persons In 25 patients with obstructive jaundice slightly positive reactions were noted in only 4 and none in the re maining 21 In contrast to the findings above strongly positive results were found in 33 of 38 patients suffering from acute hepatitis and cirrhosis In another series of cases reported the test was found to be positive in all patients with acute hepatitis cirrhosis or chronic passive congestion although the intensity of the floc culum varied considerably With improvement of the clinical con dition of the patient there was less flocculation Out of 11 patients with obstructive jaundice 9 gave slightly positive results The test was applied in another series of 284 normal persons and did not give a single false positive reaction In the same study in 455 hos pital patients without evidence of hepatic disease 3 3 per cent false positive reactions were found In 23 cases of cirrhosis of the liver

the flocculation was positive in 100 per cent in 52 jaundiced patients with hepatitis or focal hepatic lesions in 95 per cent and in 25 cases of obstructive jaundice in 70 per cent The cases of obstructive jaundice had secondary liver disturbance A strongly positive reaction was also accompanied by a reduction in the plasma prothrombin and hippuric acid synthesis

There is no doubt that the cephalin-cholesterol flocculation test offers a very sensitive and reliable index of the activity of a disease process in the liver The point worth stressing is that it does just that and cannot be taken for a measure of residual hepatic reserve In other words it is not a test of liver function Therefore absolute correlation between the cephalin cholesterol flocculation reaction and liver function tests cannot be expected since the former measures some product of active liver damage while the latter estimates the partial functions of the liver

The test has been heralded as a useful laboratory means for differentiating between obstructive and parenchymatous jaundice In that regard however it has a limited field of application It should be remembered that even though the test apparently does detect active liver damage it naturally cannot distinguish primary parenchymal disease from liver injury secondary to complicated biliary obstruction Also it cannot distinguish the obstructive phase of intrahepatic jaundice (arsphenamine hepatitis for example) from extrahepatic occlusion It is true that on statistical analysis the strongly positive results are more apt to occur in hepatocellular jaundice than in extrahepatic obstruction and consequently the test is very useful for detecting the presence of liver disease but in any one individual case it can hardly be relied upon as an infallible clue to the etiology of icterus Moreover a negative result does not *rule out hepatic disease as it may be negative in some* established cases of cirrhosis of the liver The test is useful as a prognostic aid *when repeated a number of times* on the same patient The prognosis for example is unfavorable in patients with cirrhosis of the liver when the test shows persistently strong positive reactions On the other hand, a progressive decrease in the intensity of the reaction often accompanies clinical improvement

As the sensitivity of the test depends a great deal upon the reagent used it is advisable to *standardize each preparation of cephalin* on a

group of normal subjects Further work for standardization of the test is highly desirable *

Thymol Turbidity Test This laboratory procedure was described by Maclagan (1944) who found that on addition of a saturated solution of thymol to the serum of patients with liver disease a turbidity or precipitate will result in many instances It is possible that the positive result indicates the presence of an increased amount of gamma globulin in the serum The test runs closely parallel to the serum colloidal gold reaction and the cephalin cholesterol flocculation test The positive reaction is considered by Maclagan to serve as a valuable indicator of liver dysfunction particularly in infectious hepatitis and cirrhosis The patients with parenchymal liver disease gave positive responses in a very high percentage whereas the results were either negative or only occasionally weakly positive in obstructive jaundice

HEMATOLOGICAL FINDINGS

The blood may show changes in all formed elements in the course of jaundice The hematological findings assume particular importance and are of diagnostic value in some types of hemolytic icterus Although not quite as definite and significant in other forms of jaundice they may be helpful to a limited extent from the diagnostic and prognostic standpoint

The blood changes may be classified as primary when they play a definite etiological role in the production of icterus (hemolytic anemias) and secondary when they arise as a result of jaundice or associated conditions In the first instance icterus is due to excessive hemolysis caused by some inherent defect in the red blood cells or by action of some hemolysin or poison on these cells (hemolytic septicemias phenylhydrazine favism) In the second instance the changes in the blood result from the operation of factors causing jaundice or from the presence of regurgitated bile in the blood and tissues There are several possible ways in which bilirubinemia or the conditions giving rise to jaundice may produce these changes These possibilities are (1) hemolytic effect of regurgitated bile on the red blood cells (2) effect on hemopoiesis through depletion of

* Photosensitivity has been definitely established as a cause of falsely positive reactions Therefore the test solutions should not be allowed to stand exposed to daylight during the test period.

the maturation factor normally stored in the liver (3) malabsorption of precursors of hemoglobin and plasma protein precursors from the digestive tract (4) general effects of a cachectic state incidental to some jaundiced conditions or to a malignancy (5) depressing effect of toxins primarily responsible for jaundice or resulting from impairment of the detoxifying function of the liver (6) blood loss from hemorrhage and (7) associated hypersplenism ✓

Slight to moderate transient secondary polycythemia sometimes is observed in cases of hepatitis (catarrhal jaundice) The mechanism of production of polycythemia under such circumstances is not clearly understood and the finding in general is not particularly significant. It should be remembered that a patient with either true polycythemia vera or secondary polycythemia may independently develop jaundice from unrelated causes The effect on leucocytes may be due to the presence of coexistent infection of the liver and biliary passages resulting in leucocytosis and also to the depressing effect on the leucocytes of the state of hypersplenism in conditions associated with splenomegaly

Anemia is common It may be hypochromic and/or microcytic or macrocytic Hypochromic anemia may be the result of hemorrhage from esophageal varices (cirrhosis of the liver) or result from vitamin K deficiency Hemorrhage from the latter cause is rarely severe enough to cause anemia except postoperatively In patients with malignancy a hypochromic anemia may well be expected A general depressive influence of a cachectic state incidental to the progress of jaundice of non malignant origin and malabsorption or poor intake of nutritive factors necessary for red blood cell and hemoglobin production may be the cause It has been suggested that macrocytic anemia resembling pernicious anemia encountered in some cases of cirrhosis may be due to disturbance in the storage of the hematopoietic principle in the liver This theory is contradicted by the fact that liver therapy often fails to produce a clear cut response in such patients and also by the reports that extracts prepared from the livers obtained postmortem from patients with chronic liver disease possess the anti anemic principle in amounts sufficient to produce remission in patients with Addisonian type of anemia

The changes in erythrocytes offer very little diagnostic aid if any in differentiation between parenchymal liver disease and extrahe-

patic obstruction On the other hand they acquire great importance in distinguishing hemolytic icterus from regurgitant jaundice particularly when studied in conjunction with the qualitative van den Bergh reaction

Before this aspect of diagnostic laboratory procedures is discussed it will be profitable first to review briefly certain elementary facts regarding hematopoiesis

The erythrocytes formed in the bone marrow go through a certain evolutionary stage of development before reaching the state of maturity in which they are ready to be released into the circulation The maturation process involves a progressive decrease in size of the cell the shrinkage and extrusion of the nucleus from the cell body and alterations in the staining reaction of the cytoplasm which changes from basophilic (staining blue with the Wright s stain) to acidophilic (staining yellowish red with the same stain) when the cell develops its full complement of hemoglobin The nucleated red cell with blue cytoplasm is termed a basophilic normoblast the one with yellowish red cytoplasm an acidophilic (or orthochromatic) normoblast and the intermediate cell with the first faint blush of hemoglobin a polychromatic normoblast With supravital technic which involves the application of certain dyes such as brilliant cresyl blue to a fresh blood preparation a flaky precipitation of the basophilic substance occurs appearing as a reticulum Hence the name of reticulocyte applied to red blood cells with such an appearance

In health the overwhelming majority of erythrocytes released from the bone marrow into the circulation are perfectly mature They possess no nucleus or basophilic substance in their cytoplasm In normal individuals only about 1 per cent of red blood cells found in the circulating blood are reticulocytes However whenever there is loss of blood from any cause and therefore increased demand on the bone marrow for replenishment of blood reserve a greater number of immature red cells are released into the circulation as if in a hasty attempt on the part of the bone marrow to make good the loss sustained Under such circumstances a greater percentage of immature erythrocytes—normoblasts and reticulocytes—is found in the blood In congenital hemolytic icterus such an increase in reticulocytes at times is amazing particularly during crises and may reach proportions hardly ever attained in any other condition

There are two other hematological findings of importance often

found in association with the one mentioned above changes in (1) the shape of the erythrocytes and (2) their state of fragility A normal mature red blood cell has usually the shape of a biconcave disc In congenital hemolytic icterus some erythrocytes are smaller than others assuming a spherical form These spherocytes are fairly characteristic of the disease It is perhaps by virtue of their shape that these cells exhibit a lowered resistance to hemolysis in decreasing strength of hypotonic salt solutions This may be due to the fact that cells with a spherical shape need to absorb very little fluid to bring them to the form in which their membrane is stretched to the bursting point Increased fragility in hypotonic saline solutions is unusual in other forms of hemolytic anemia It may be observed in some cases of the acquired type especially in acute cases In some forms of hemolytic anemia (sickle cell disease) the fragility in fact may be even decreased (increased resistance to hemolytic effect of hypotonic solutions)

The erythrocyte fragility test is based on the fact that the normal red blood cells offer a certain resistance to the disintegrating effect of hypotonic solutions Only a slight lowering of the osmotic pressure of the surrounding medium will not produce hemolysis The normal concentration of salts in human plasma is approximately 0 94 per cent Normal cells may be placed in a 0 6 per cent saline solution without being hemolyzed and although the cell may increase in volume it will not do so to the point of rupturing the membrane Normally hemolysis commences when the saline concentration is reduced to about 0 45 to 0 40 per cent and is complete at 0 34 to 0 30 per cent The resistance that red blood cells offer to the hemolytic action of hypotonic solutions is thus used to test their fragility 0 2 cc of blood is measured into each of a series of tubes containing in a graded series various concentrations of salt solution The slightest trace of red color in the supernatant fluid indicates the destruction of the least resistant cells Complete hemolysis is indicated by a clear red solution and the absence of a residue of intact cells in the bottom of the tube or the absence of any degree of cloudiness when the tube is gently shaken

In a patient with jaundice the indirect van den Bergh reaction (negative direct positive) spherocytosis increase in reticulocyte count and decreased fragility of red blood cells all point unmistakably to congenital hemolytic icterus

While leucocytosis is found in the presence of an associated infection (cholecystitis cholangitis etc) leucopenia may be a marked feature throughout the course of jaundice associated with splenomegaly (splenomegalic cirrhosis) Attempts have been made to distinguish between different causes of the regurgitation type of jaundice by means of total leucocyte and differential counts In the differential diagnosis of jaundice absolute reliance upon such data is not justifiable

Parenchymal liver disease may be associated with thrombocytopenia which is quite marked in some instances (15 000 to 20 000 platelets per cu mm of blood) Hemorrhagic tendencies in such cases may be due not only to vitamin K deficiency but also in part to thrombocytopenia However the latter is far from being constant and even though many patients with chronic hepatitis tend to have a decreased platelet count (100 000 to 200 000 per cu mm of blood) this finding can hardly be used in the differential diagnosis The platelet count has a tendency to increase quite markedly with clinical improvement in cases where initially very low counts are observed Thus in a number of cirrhotic patients the author has observed marked and rather rapid increase in platelets coincident with spontaneous diuresis loss of ascites and other signs of amelioration in the general condition of the patient

CHOLECYSTOGRAPHY

Cholecystography has only a limited place in the differential diagnosis of jaundice In the presence of icterus even a normal gall bladder will often fail to visualize on administration of the dye The reason for this is evident if one keeps in mind the steps involved in this test On reaching the small intestine the gall bladder dye is absorbed through the mucosa and enters the portal blood stream It is then carried to the liver where the hepatic cells excrete it with the bile which enters the bile canaliculi then the hepatic duct and finally through the cystic duct reaches the gall bladder There the dye laden bile is concentrated and sufficient dye is now present to render the gall bladder radio-opaque It is obvious that the diseased liver will fail to excrete properly both the bile and the dye and the latter will be removed by the liver from the circulation to only a limited extent if at all

Radiographic scout films of the abdomen reveal only a small percentage of gallstones About 3 per cent of biliary calculi contain enough calcium to be radio-opaque and thus directly visible without a contrast medium Calcium free stones are demonstrable only as transluscent areas (filling defects) if the dye laden bile surrounding them is sufficiently dense Thus in a case of jaundice that is possibly due to a common duct stone very little help will be derived from a plain radiographic scout film of the abdomen for three reasons (1) there may not be any stones present in the gall bladder itself (2) if present the chances of visualizing them are very small and (3) even demonstration of stones in the gall bladder area does not necessarily establish the diagnosis of a common duct calculus as jaundice may be of an entirely unrelated etiology It is estimated that about 10 per cent of the population have gallstones When the stones are accidentally discovered they often constitute an unrelated finding and are asymptomatic

Duodeno-Biliary Drainage

With Meltzer s observation that a 25 per cent solution of magnesium sulphate relaxes the duodenal mucosa and thus promotes drainage of bile from the biliary tract into the intestine a new era in biliary tract diagnosis was inaugurated The introduction of duodeno biliary drainage by Lyon and its refinement by Rehfus made a useful application of this knowledge and made it possible to obtain fractions of bile from the several levels of the biliary tract This has helped materially in evaluation of the pathological changes and dysfunction of the biliary system

The evacuation of the biliary contents following the introduction into the duodenum of a 17 to 33 per cent solution of magnesium sulphate or 10 per cent solution of peptone or olive oil affords the opportunity to study separately the different fractions of the bile known as A B and C The first bile from the common duct with some admixture from the cystic duct and perhaps some freshly secreted liver bile constitutes the A fraction The B fraction that follows is distinguished from the first sample by a deepening of the color to golden yellow or mahogany and a more syrupy consistency It is derived from the gall bladder as shown by a vastly greater concentration of biliary constituents Thus bilirubin is present in the

'B' sample in a concentration 30 to 50 times that of the 'A' fraction The thinner lemon yellow bile ('C' fraction) that follows is the bile freshly secreted by the liver cells The failure to obtain the 'B' fraction demonstrates occlusion of the cystic duct by some pathological process, such as inflammation or obstruction by a gallstone or adhesions However, atony of the gall bladder may also result in failure to obtain B bile

The material obtained from duodenal drainage is examined for (1) physical properties, such as color and viscosity, (2) mucus epithelial cells pus and blood constituents, (3) crystals (cholesterol, calcium bilirubinate), (4) bacterial culture (5) parasites (giardia and ascaris), (6) presence of duodenal ferments, (7) chemical examination, with special reference to bile pigment, cholesterol and bile salt concentration

It is important to ascertain the presence or absence of bile pigment for obvious reasons Of great importance is also the presence or absence of bile salts since the liver may be capable of excreting bile pigment when it is not able to synthesize or excrete bile salts A shift in the bile salt partition in favor of desoxycholic acid is regarded as diagnostic of biliary tract infection or liver damage While roentgenological studies of the gall bladder may fail, the presence of cholesterol and calcium bilirubinate crystals suggests the existence of gallstones in the common bile duct or gall bladder Gallstone 'dust may be found in the material In acute hepatitis lightly pigmented bile may be found devoid of crystals Blood may suggest an ulcerating carcinoma of the ampulla of Vater For determination of occult blood in the duodenal contents of the stool, the guaiac reaction is more useful than the benzidine test because the former is the more specific of the two Therefore, while a 1 + result with the guaiac test is significant a 1 + result with the benzidine test may be disregarded Nonvisualization of the gall bladder by x ray may be of no significance because it may be the result of inadequate elimination of bile, unless it is accompanied by positive findings on crystallographic study When epithelial debris pus cells and bacteria are found in abundance a catarrhal inflammation of the duodenum or biliary ducts (cholangitis) is suspected However, the same findings may be present in patients with gastric anacidity and pancreatic disease In acute bacteremic cholecystitis and typhoid carriers bile culture yields significant results Great care must be exercised

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the right upper quadrant of the abdomen has also been used Lately a special needle devised primarily for tumor biopsy (Vim Silverman needle) has been introduced The area of skin selected for the needle insertion through the anterior approach is prepared with antiseptic solution and draped Infiltration is carried out with a local anes thetic down to the parietal peritoneum A small skin incision is made to facilitate the passage of the needle through the abdominal wall Its entrance into the liver is signaled by its movement coinci dent with respiration Then suction is applied for aspiration of liver tissue The risk of bleeding from the surface of the liver is not very great but should be kept in mind As a routine precaution the bleeding time clotting time and prothrombin time determinations of each patient to be subjected to biopsy are recommended the pres ence of any serious bleeding tendency passive congestion of the liver suspected liver abscesses or suppurative cholangitis are deemed a contra indication The procedure is best reserved for enlarged and easily palpable livers If it is desirable to have a biopsy in a patient with a small or a normal sized liver peritoneoscopy should be the method of choice

Peritoneoscopy

A procedure that has proved to be of great value in the study of jaundice is peritoneoscopy Briefly the technique consists of first inducing a pneumoperitoneum An illuminating endoscope is then introduced into the inflated abdominal cavity and the viscera are examined thus the anterior peritoneal wall the liver and gall blad der the anterior part of the stomach the coils of intestine and the urinary bladder may be scrutinized as well as the spleen if it is enlarged In the female the pelvic organs may also be seen Speci mens of suspicious tissues can be removed by means of a specially designed biopsy forceps

Peritoneoscopy usually provides positive diagnostic information in those cases of jaundice that are accompanied by hepatomegaly Metastases and implants on the liver and peritoneum stand out prominently and are easily recognized One of the nodules may be biopsied and the growth examined histologically Cirrhosis pro duces a characteristic scarred liver Biopsy will further confirm the diagnosis If ascites is present the procedure is all the more easily

in carrying out bacteriological studies because of ease of contamination

Duodenal drainage should not be attempted in the presence of acute cholecystitis serious cardiovascular disease debility acute pancreatitis and recent hemorrhage Frequently the patient is too ill to be subjected to the procedure It requires considerable skill and experience for proper execution

Hepatolienography

Visualization of the liver and spleen is made possible by the ability of the reticulo endothelial cells in these organs to fix colloidal substances Upon intravenous injection of thorotrast which although radioactive is a relatively harmless compound visualization of the liver and spleen is effected by radio opaque deposits of this substance It is claimed that this procedure is of great aid in the diagnosis of metastatic carcinoma of the liver

Liver Biopsy

It is possible to aspirate the liver in order to obtain material for histological study The needle biopsy sometimes permits accurate diagnosis in instances where laboratory and clinical findings are inconclusive Apparently the procedure was first employed as far back as 1885 without however fixing and staining the material obtained and therefore the examination of the tissue could not permit an accurate diagnosis One of the most extensive series of needle biopsies of the liver employing modern methods of tissue fixation and staining was reported in 19°3 The most important advance in the use of liver biopsy arose from the studies of Iverson and Roholm whose method consisted of a posterior lateral approach to the liver in the ninth intercostal space of the right posterior axillary line with a needle 18 cm long and 2 mm in width The needle is inserted through the pleura and the diaphragm and carried into the liver The pointed obturator is then removed from it leaving the serrated cutting edge of the needle embedded in the posterior liver surface A small plug of tissue is removed by drawing it up into the needle by means of suction applied through a syringe attached to the needle hub The anterior approach through

ing different activities of the organ are used conjointly and with judicial repetition

The tests associated with diverse activities of the liver are more useful than are several that probe a single function The liver has many activities and each of the methods tests a different performance of the organ In the case of a patient with suspected hepatic damage or in a patient in whom the diagnostic problem may be elucidated by demonstrating the absence of such damage the study should include the procedures designed to probe the excretory capacity of the liver its detoxifying abilities its metabolic functions in regard to carbohydrate metabolism and such studies as the cholesterol flocculation test the albumin/globulin ratio and measurements of the serum bilirubin The bilirubin excretion test proves the capacity of the liver to excrete into the bile a normal constituent of the bile while the azorubin S test determines its capacity to excrete a foreign dye into the bile The bromsulphalein test measures the ability of the reticulo endothelial system of the liver (Kupffer cells) to fix a foreign dye The hippuric acid test measures the efficiency state of the detoxifying power of the liver in the synthesis of glycine and its conjugation with benzoic acid to form hippuric acid The galactose or glucose tolerance test probes other aspects of the enzymatic system of the organ i e the glycogenic activity of the liver The amino acid test determines the deaminifying power of the liver while the prothrombin response to vitamin K tests the power of synthesis The albumin/globulin ratio or ester cholesterol partition also offers some measure of the same function The cephalin cholesterol flocculation test does not measure any functional capacity but reflects the general state of liver damage and perhaps its extent

The results of these various laboratory procedures do not run parallel Whereas in far advanced stages of liver disease perhaps all liver function tests are abnormal in instances of lesser degree of liver damage the impairment is usually selective so that the functional state of *the liver is better ascertained by using a number of* different tests One has only to consider the multiplicity of hepatic activities to realize that any single laboratory procedure can hardly be expected to reveal everything about the functional state of the organ Only from the composite picture presented by an array of various tests correlated with the general condition of the patient

done and the patient is relieved of his fluid at one sitting Acute hepatitis and acute liver atrophy can be diagnosed after biopsy Un common diseases such as hemochromatosis and the xanthomatosis cannot usually be diagnosed positively without histological study of the biopsied specimen

A carcinomatous gall bladder is shrouded in a matted mass of tissues and therefore cannot be seen but its metastases can be detected Stones within the biliary system and growth of the pancreas cannot of course be seen through the peritoneoscope In the differential diagnosis between silent stones of the biliary system and carcinoma of the head of the pancreas peritoneoscopy is of little aid except in ruling out other possibilities

Peritoneoscopy should not be attempted when abscess of the liver or any other suppurative intra abdominal disease is suspected lest the infection be spread by instrumentation Needless to say the procedure should not be attempted when other simpler studies will lead to a diagnosis

EVALUATION OF THE LABORATORY TESTS EMPLOYED IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

The diagnosis of diseases of the liver and biliary tract is based largely on clinical grounds laboratory procedures are rather limited in value However the tests do offer some aid and are at times indispensable for diagnosing difficult cases

The most useful field of application of various liver function tests *is in the detection of early functional disturbances of the liver* in the subclinical and early stages of the disease However the tests fail to distinguish between acute and chronic forms of liver damage or dysfunction nor can they reveal the nature of the etiological agent Whether the damage is due to an infectious agent or a poison or *is secondary to persistent biliary obstruction* cannot be determined by these means The tests are helpful in following the progress of the disease and the progression or regression of pathological processes in the liver in determining the risk of surgical procedures in directing medical treatment or the preoperative and *postoperative treatment in surgical cases* and in rendering prognosis In addition they may furnish some estimate of the functional capacity of the liver particularly when laboratory procedures test

in liver disorders impaired glycogenic function as shown by the ability to metabolize galactose usually comes later than impaired clearance of bromsulphalein excretion of azorubin-S or bilirubin, or synthesis of hippuric acid On the other hand other studies point to bilirubin excretion or hippuric acid tests as most sensitive Some workers find the bromsulphalein more sensitive than the hippuric acid test others find the reverse etc The sensitivity of the tests is ranked differently by different investigators The want of agreement between the various reports arises in part from the differences in technique the limited number of cases studied in the various groups and the variations in the types of cases studied.

The important effect of age is also frequently lost sight of The estimation of function that could be assumed to be abnormal in younger persons (those under 55 or 60 years of age) may be usual in the individual above this age It is reasonable to assume that in common with the general changes incidental to aging some alterations in structure and function occur also in the liver Another important determinant is time The large factors of safety and capacity of regeneration are the limiting elements in the use of liver function tests and unless the hepatic damage is both rapid and extensive, simultaneously occurring regenerative processes may compensate for and mask the effects of destructive pathological processes Opinions concerning the practical usefulness of liver function tests vary all the way from those investigators who place great reliance upon them to those who find them of little value as a guide to diagnosis prognosis or treatment.

The liver function tests have not proved so far to be as successful as the physician would like them to be in corroborating the clinical diagnosis of hepatic disease They depend on too many variable factors and do not always give the desired information the results sometimes being ambiguous Moreover, some of the more reliable procedures are too complicated or expensive for general use, unless they are done in a large hospital Their limitations are minimized however by employment of multiple tests their repetition at certain intervals and their correlation with the clinical state and course of the disease

Granted that the liver function tests do have a place in the diagnosis of liver disease the question arises What can be expected from them in the differential diagnosis of jaundice? In regard to

can insight be gained in regard to the nature of the disease process

The interpretation of results may be difficult Usually, positive readings are much more significant than negative ones, as the latter do not necessarily exclude liver disease This statement, however, must be made with certain reservations Normal results of the various liver function tests carried out simultaneously may be very significant in a case of suspected liver damage, since serious hepatic injury is not likely to exist if all test substances employed react normally It is true, nevertheless, that in some instances the patient's state may be grave while some one particular hepatic function remains within normal limits This should caution us that even the most accurate of tests must be permitted a reasonable margin of error and that the latter is possible because of the amazing reserve capacity of the organ Such enormous reserve allows for the presence of even a serious pathological process, while some hepatic function or functions remain unimpaired, at least in accordance with the available standards of measurement Often it is very difficult if not impossible, to correlate all the findings properly This results again from the fact that the activities of the liver are not impaired equally under various conditions, so that a dissociation of hepatic function may occur Thus a liver that is performing rather normally in regard to certain activities may at the same time be markedly impaired in carrying on its other functions Hence, the obvious need for performing several tests measuring different functions of the liver No less important is a judicious repetition of these tests, for the liver is not a static organ, and its dynamic state must be kept in mind Liver function varies, not only from day to day, but also from hour to hour

There is no unanimity of opinion with regard to the relative merits of the numerous tests employed For example some workers consider the galactose tolerance test more valuable than the glucose tolerance, and vice versa It is also felt that some hepatic activities may be affected earlier than others so that tests designed for measurement of those functions that are presumably affected first are more valuable in determining the incipient or early stages of hepatic impairment than others There is no agreement, however, on the precise order in which various hepatic capacities are affected in disease, or even on the fact that such a sequence of events may be always constant Thus, many studies seem to indicate that

In the use of liver function tests as aids in the differential diagnosis between obstructive and hepatocellular jaundice the cardinal considerations are (1) the stage of intrahepatic obstruction in parenchymal liver disease (2) the possibility of secondary hepatitis developing in the course of biliary obstruction In the former instance the laboratory findings are indistinguishable from those in the case of gross mechanical obstruction of extrahepatic ducts for example postarsphenamine jaundice

During the obstructive phase of parenchymal liver disease associated with hepatic degeneration there is less marked degree of functional impairment of the liver as revealed by liver function tests than in the case of hepatic involvement secondary to long standing extrahepatic biliary obstruction This is explained by the fact that liver cells regenerate anew more readily in the former case where the obstruction is recent whereas in the latter instance the tendency to regeneration is much less marked or altogether negligible Usually the liver itself is not disturbed markedly early in the course of biliary obstruction and this is the time when liver function tests may be helpful Unfortunately parenchymal injury not only always develops eventually in the course of obstructive jaundice but in fact may appear early in the course of the disease and thus greatly confuse the clinical picture On the other hand obstruction may be incomplete and of short duration and thus produce little change Whereas the liver itself may not be damaged in the early stages of extrahepatic obstruction and the results of liver function tests are then negative in hepatocellular jaundice there frequently are early and serious enough disturbances of some of the hepatic functions to be reflected in positive readings on various tests

For the reasons mentioned above all the tests used in the differential diagnosis of jaundice must be given with the time element in mind While in uncomplicated forms of icterus of short duration rather definite and clear-cut results can be expected in cases of long standing jaundice the picture presented by composite tests may be confusing

The purpose for which a particular test or set of tests is to be used is of great importance Before ordering any of these laboratory procedures the physician should ask himself the following questions (1) Is the test intended to reveal subclinical liver disease?

these laboratory procedures, more attention has been directed by the clinician to hepatic function than to the cause of icterus Be cause these tests are usually designed to throw a *maximum load on* a liver function, they may reveal its disturbance long before per formance has declined sufficiently to produce clinical signs and symptoms Once jaundice becomes apparent, the disease process is well established Can the tests also distinguish between the differ ent types of jaundice? As far as certain well established forms of hemolytic icterus are concerned, the tests with the exception of the van den Bergh reaction, are not necessary for establishing the diag nosis and merely offer a confirmatory piece of evidence For example, quantitative estimations of urobilinogen in the urine and feces will reveal a marked increase in its elimination But, under the circum stances one hardly needs to know the exact values as the diagnosis can be definitely established on other grounds In cases of hemo lytic icterus complicated by hepatic injury or biliary calculi, the story is of course different, and the diagnosis may present some stumbling blocks

Can these tests distinguish between obstructive and parenchyma tous forms of jaundice? The significance of the results will depend on whether or not the liver is damaged in biliary obstruction A factor of primary consideration is the duration of the disease There exists a close interrelation between the intrahepatic and extra hepatic disease processes There is never gross obstruction to the extrahepatic bile ducts without some injury to the liver, and con versely, there is never a pure hepatic form of jaundice *without* dam age or obstruction to the intrahepatic biliary canaliculi during some stage of the disease The liver is frequently injured in obstructive jaundice of several weeks' duration, in which case the tests are not very helpful if they give positive results On the other hand, under the circumstances, demonstration of *normal liver function* by mul tiple tests is strongly diagnostic of extrahepatic obstruction The time element also is important in so far as regeneration is con cerned For example, in acute *hepatitis, negative results* may be obtained with certain tests if their performance is delayed until *regenerative processes* have had time to set in Thus, in hepato-genous jaundice, functional disturbances may at times be difficult to detect, as the initial injury may be quickly repaired, producing little evidence of dysfunction at any time

TABLE VII

LABORATORY TESTS IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

Procedure	Normal Values	Uncomplicated Complete Obstructive Jaundice	Uncomplicated Parenchymatous Jaundice	Uncomplicated Hemolytic Jaundice
1 Duodenal drainage				
a. Bilirubin	+	−	+	+++
b. Blood	−	+ (carcinoma)	−	−
c. Crystals—cholesterol and bilirubinate	±	++ (cholelithiasis)	±	±
d. Epithelium and pus	±	±	++ (cholangitis)	±
2. Urine				
a. Bilirubin	−	+++	+	−
b. Urobilinogen	0-4 mg./24 hrs	−<0.5 mg	+++0.5-100 mg	++5-30 mg
3 Feces				
a. Bilirubin	+	−	+	+++
b. Urobilinogen	40-280 mg./24 hrs	−<5 mg	+10-300 mg	+++ 600-1,000 mg
c. Blood	−	+(carcinoma)	−	−
4. Blood				
a. Icterus index	<6 units	+++50-200	++6-150	+>6
b. Quantitative bilirubin	0.25-0.5 mg %	+++(slow rising)	++(rapid ↑ and ↓)	+(crises)
c. Van den Bergh	indirect (faint)	immediate direct	delayed direct	indirect (intense)
d. Phosphatase	<4-6 units	+++13-1 0	++2.8-33.4	−2.6-13.4
e. Cholesterol—				
Total	145-285 mg %	+++109-511	variable 73-342	normal
% free	26-33%	+++29-99	++25-95	normal
f. Prothrombin—% of normal	90-100%	++ 8-75%	++41-76%	normal
Response to therapy	−	++(+8) (+62)	−(−34) (+10)	normal
g. Other findings	−	progressive anemia (carcinoma)	leucocytosis (cholangitis)	anemia reticulocytosis fragility
5 Other liver function tests				
a. Galactose—oral	<3 gms	−(early) 0-2.2	++(early) 1.8-6.4	
Intravenous	0 at 75′	−<.02-.68(13.5)	++>.203 .145(48)	−
b. Hippuric acid—oral	2.6-3.3 gms	−2.6-3.4	++0.52-3.06	−
Intravenous	0.7-0.95 gms.		++0.27-0.74	−
c. Cephalin flocculation	− or +	− or +	+++ or ++++ (prompt)	− or +

− absent or normal + present ± trace absent or present ++ to ++++ increased

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(2) *Is it to be made for the evaluation of the progress of the disease* and measurement of the speed and degree of recovery of liver function? (3) Is it to ascertain the activity of the disease process or regeneration and thereby assist in the management of the case and the prognosis? (4) Is it to assist in distinguishing between the obstructive and parenchymatous jaundice, *or is it merely to aid in the* detection of hepatic dysfunction?

If the problem in question is the differential diagnosis of jaundice, what tests are most helpful? In distinguishing hemolytic icterus from all other types of jaundice, the van den Bergh reaction in conjunction with certain hematological studies, is the test of paramount importance As to differentiation between the various forms of regurgitant jaundice, the decision regarding the question of what *tests would be most useful seems to be largely* a matter of opinion It does appear, however, that a few tests do possess more definite value than others These are the response of subnormal plasma prothrombin to the administration of vitamin K and the quantitative determinations of urobilinogen in the urine and feces To these laboratory procedures others may be added under certain circumstances galactose tolerance or hippuric acid synthesis tests and duodeno biliary drainage

Tests Useful in the Differential Diagnosis of Jaundice

1 *Van den Bergh reaction*
2 Quantitative urinary and fecal urobilinogen tests
3 Blood prothrombin (vitamin K response)
4 *Galactose tolerance test*
5 Hippuric acid synthesis test (preferably intravenous method)

The use of liver function tests is to be encouraged, but only when their limitations are well understood and constantly kept in mind

A pessimistic attitude in regard to liver function tests is not justifiable It is unfortunate that these tests have in a large *measure been neglected*, and strangely enough have been held in disrepute more by the internist than the surgeon Through bitter experience gained from observation of stormy postoperative courses and unnecessary deaths the surgeons have come to respect these *tests* They realize *that with these* laboratory procedures at their command, such unfortunate happenings can be prevented The surgeons

Gutman A B Olson K B Gutman E B and Flood C A *J Clin Invest*, 19 129 1940
Hanger F M *J Clin Invest* 20 241 1939
Hanger F M and Gutman A B *J A M A* 115 263 1940
Harding V J and Van Nostrand F H *J Biol Chem* 85 765 1929
Harrison G A. *Chemical Methods in Clinical Medicine* London J and A Churchill 1937
Harrop G A and Barron E S G *J Clin Invest* 9 577 1931
Hawkinson V and Watson C J *J A M A* 129 514 1945
Hoffbauer F W Evans G T and Watson C J *Med Clin N America* 29 363 1945
Holbrook, A A *Am J Digest Dis and Nutr* 3 315 1936
Hough V H and Freeman S *Am J Physiol* 138 184 1942
Iverson P and Roholm K *Acta Med Scandinav* 102 1 1939
Ivy A C and Roth J A *Northwest Univ Med. School Quart Bull* 17 178 1943 ibid. 17 190 1943
Jacobi H G *Am J Digest Dis and Nutr* 4 162 1937
Lichtman S S *Diseases of the Liver Gallbladder and Bile Ducts* Philadelphia Lea & Febiger 1942
Lucatello L. *Lavori del Congressi di Medicina Interna* Rome 1895 p 327
Maclagan N F *Brit J Exper Path* 25 234 1944
McMaster P S and Elman R *J Exper Med* 43 753 1926
Mateer J G Baltz J I Marion D F and Macmillan J M *J A M A* 121 723 1943
Moser R. H Rosenak, B S and Hasterlick R. J *Am J Digest Dis and Nutr* 9 183 1942
Myers C P *J Indust Hyg and Toxicol* 27 52 1915
O Leary P A Green C G and Rowntree L. G *Arch Int Med* 44 155 1929
Pohle F J and Stewart, J K *Am J Med Sci* 198 622 1939 *J Clin Invest* 20 241 1941
Progress of Medical Sciences *Am J Med Sci* 208 661 1915
J *Proc Soc Exper Biol and Med* 29 1204 1932 *Am J Med Sci*, 1933
D H *Arch Surg* 43 231 1941
H and Soskin S *Ann Int Med* 132 1611 1940
I Soskin S *Am J Digest Dis and Nutr* 8 421 1941
Soskin S *Ann Int Med* 13 1044 1940 *Am J Dig* 1941
E. C. *J A M A* 84 1112 1925
J Exper Med 41 601 1925
R. *J Exper Med* 41 601 1925
E. *Proc Staff Meet Mayo Clinic*, 18 252 1943
J Dig Dis, 5 597 1938
M A. *Arch Int Med* 47 391 1931
Obst, 63 596 1936

are aware of three fundamental facts (1) presence of liver damage increases surgical risk (2) such liver damage may exist in a sub clinical state in individuals who ordinarily would not have been suspected of having an injured or constitutionally weak liver (3) once the weak spot is discovered by proper preoperative and post operative care the surgical risk is materially decreased There are individuals who can be considered as liver weaklings and while their hepatic function is adequate for the stress and strain of ordi nary life it cannot withstand the added strain of surgery Unless provisions are made for their weak spot they may lose their lives It is time for the medical man to take a lesson from the surgeon and become more liver and liver function test conscious

BIBLIOGRAPHY

Allen J G *Gastroenterology* 3 502 1944

Allen J G *Gastroenterology* 3 490 1944

Althausen T L B skind G R and Kerr W J *J Lab and Clin Med* 18 954 1932

Banks B M Sprague P H and Snell A M *J A M A* 100 1987 1933

Barron E *Arch Int Med* 63 276 1939

Bassett A M Althausen T L and Coltrin G *Am J Digest Dis and Nutr* 8 432 1941

Bauer R *Wien med Wchnschr* 56 2537 1906

Bingel A *Verhandl d Deutsch Gesellsch f inn Med* 35 210 1923

Bockus H L Shay H Willard J H and Pessel J F *J A M A* 96 311 1931

Bodansky M and Bodansky O *Biochemistry of Disease* New York The Macmillan Co 1940

Bodansky A and Jaffe H L *Proc Soc Exp Biol and Med* 31 1179 1934

Cantarow A and Wirts C W *Proc Soc Exp Biol and Med* 47 252 1941

Chiray M and Marcotte A *Bull mem Soc med hop de Paris* 1 696 1930

Coller F A and Jackson H C *J A M A* 112 128 1939

Colp F A and Doubilet H *Arch Surg* 33 913 1936

Cori C F *Proc Soc Exp Biol and Med* 23 459 1925

Eagle H *Medicine* 16 95 1926

Elton N W *J Lab and Clin Med* 17 1 1931

Epp nger H *Die Leberkrankheiten* Jul us Springer Wien 1937

Franke K *Med Klin* 27 94 1931

Gray S and Barron C G *J Clin Invest* 22 191 1943

Gray S J *Proc Soc Exper B ol and Med* 41 470 1939

Greenberg, J R Personal communication

Greene C H Plotz M and Localio S A *Arch Int Med* 61 608 1938

Greene C H Shattuck H F and Kaplowitz L *J Clin Invest* 13 1079 1934

DIFFERENTIAL DIAGNOSIS OF JAUNDICE—GENERAL PRINCIPLES

THE classification of jaundice on the basis of pathological physiology has been extensively discussed in Chapter IV Rich s classification (1930) into two general groups—retention and regurgitation types—rests upon sound premises However from a practical point of view it is inadequate for a number of reasons In the first place the regurgitation type includes several distinct forms of jaundice a clear differentiation between them is of paramount importance to the clinician from the standpoint of both prognosis and therapy Secondly a more meaningful orientation for the purpose of clinical practice is made possible by a different grouping of all cases of jaundice that takes into consideration certain clinical features of practical importance In spite of its merits Rich s classification has no therapeutic intent It was designed by a pathologist not a clinician This purpose of therapeutic intent is well served by McNee s classification (1923) He divides jaundice into three distinct classes (1) obstructive hepatic jaundice which implies mechanical interference with the flow of bile through the extrahepatic channels (2) toxic or infectious jaundice which implies injury of the hepatic cells by toxic or infectious agents and (3) hemolytic jaundice which implies an increased rate of destruction of the red blood cells and a resulting production of bilirubin beyond the excretory capacity of the liver

This classification calls for several comments Toxic or infectious jaundice due to parenchymal liver injury is associated at least during some stage of the disease with obstruction of the biliary canaliculi within the liver itself The intrahepatic obstruction may at times be practically as complete as in cases due to mechanical occlusion of the extrahepatic biliary passages This feature of paren

Snell, A. M *Canad M A J*, 37 318, 1937
Snell, A M, and Magath, T B *J.A.M A*, 110 167, 1938
Soffer, L. J *Medicine*, 14 185 1935
Sparman, R *Arch Int Med*, 63 872, 1939 ibid 63 872, 1939
Steigman, M S, and Dyniewicz J M *Gastroenterology*, 1 855 1943
Stokes J, Jr and Neefe, J R *J A M A*, 127 144 1945
Thannhauser, S J, and Anderson, E *Deutsch, Arch f Klin Med*, 137 179 1921
Thannhauser, S J, and Schaber, H *Klin Wchnschr*, 5 242, 1926
Terwen, A J L. *Deutsch Arch f Klin Med*, 149 72, 1925
Watson, C J *Am J Clin Path*, 6 458, 1936, *Arch Int Med*, 59 196 1937 ibid. 59 206 1937
Watson, C J *Ann Int Med*, 12 1782, 1939
Watson, C J *J A.M A*, 114 2427, 1940
Watson C J *New England J Med*, 227, 705 1942
Watson, C J *Wisconsin Med J*, 43 1033 1944
Watson, C J and Bilden E *Arch Int Med*, 68 740 1941
Watson, C J, Schwartz, S, Sborov, V, and Bertie, E *Am J Clin Path*, 14 605 1944
Watson C J *Wisconsin Med J*, 43 1033 1944
Waugh, T R *Am J Med Sci*, 200 655 1940
Weir J F *Med Clin N America*, 29 973 1945
Weiss, S *Clinical Lectures on the Gallbladder and Bile Ducts*, Chicago The Year Book Publishers Inc., 1944
White F W *New England J Med*, 1936
Wilenski A O *J Internat Coll Surg*, 7 50 1944
Wintrobe, M M, and Shumaker H S *Bull Johns Hopkins Hosp* 52 382 1933
Wirts C W, and Cantarow A *Am J Digest Dis*, 9 101, 1942
Yater W M, and Otell, L S *Ann Int Med*, 7 381, 1933

comprehension and employment a more exact knowledge of the fundamental pathology of jaundice than an average practitioner has at his command One would heartily agree with the first clause, as the older classification of McNee is undoubtedly the most practical of the two Nevertheless Rich s classification has sound premises and it would be unwise from anyone s point of view to surrender it to oblivion Anyone interested in jaundice should also take the trouble of probing into the pathological physiology and mechanism of its production These problems were so clearly elucidated by Rich some fifteen years ago that very little of fundamental importance has been added to it since Convenience and simplicity cannot always compensate for sound and thorough knowledge

From the practical point of view McNee s classification can be elaborated upon In accord with the diverse management required in different types of jaundice included in the group of extrahepatic obstruction the latter may be classified into two subgroups (1) calculous and (2) cancerous It is true that there are certain causes of obstructive jaundice such as stricture of the common duct and chronic pancreatitis which are not readily included in these subdivisions However such conditions are relatively rare and the vast

TABLE VIII

CLASSIFICATION OF JAUNDICE

<table>
<tr><th colspan="3">Clinical classification of jaundice</th><th>Classification of jaundice on the basis of pathologic physiology (Rich)</th></tr>
<tr><td colspan="3">Hemolytic icterus</td><td>Retention jaundice (acholuric)</td></tr>
<tr><td rowspan="2">Hepatogenous jaundice (parenchymatous, hepatocellular)</td><td colspan="2">infectious</td><td rowspan="5">Regurgitation jaundice</td></tr>
<tr><td colspan="2">toxic</td></tr>
<tr><td rowspan="3">Obstructive jaundice</td><td rowspan="2">benign</td><td>calculous</td></tr>
<tr><td>stricture</td></tr>
<tr><td colspan="2">malignant</td></tr>
</table>

chymatous jaundice has been alluded to previously The block in the hepatic filter arising in the course of liver involvement had also been recognized by McNee Thus obstructive jaundice strictly speaking includes both the intra and extrahepatic varieties of obstruction However common usage has so long attached to the term of obstructive jaundice the limited implication of me chanical occlusion of extrahepatic biliary channels that we may feel justified in retaining it in that sense without serious confusion

On the other hand extrahepatic occlusion eventually leads to secondary parenchymatous liver damage from the obstruction and secondary infection It has been estimated that about two thirds of the patients with extrahepatic obstruction have hepatic lesions that are transient and relatively minor and offer no great obstacle to recovery while in the remaining third there exist various degrees of degenerative or destructive lesions of the parenchyma of the liver proliferation of connective tissue and cirrhosis cholangiectasis and cholangitis—all associated with disturbance of liver function

With regard to hemolytic icterus the reader is reminded that to the factor of overproduction of bilirubin is added hepatic injury or dysfunction with the result that the combined operation of these two processes rather than either one of them alone is respon sible for the retention of an abnormal amount of bile pigment in the blood stream In many instances of hemolytic jaundice there may be added still another factor—that of extrahepatic obstruction by biliary calculi which individuals with such disorders are so prone to develop In other words it is the mixed type of jaundice that is commonly encountered in clinical practice rather than one of the pure forms mentioned in McNee s classification

No matter what classification is used it is now generally ac cepted that jaundice will occur whenever there is a disturbance be tween the amount of bilirubin delivered to the liver for excretion and the capacity of the liver to excrete the pigment delivered to it With this consideration is coupled the question of the integrity of intra and extrahepatic biliary passages Perhaps McNee s classifica tion helped to change Minkowski and Naunyn s original statement without the liver no jaundice into Aschoff s later statement with out defective excretion of biliary pigment via the liver no jaundice

It has been said that Rich s classification is not well adapted to the needs of the average practitioner and that it requires for its

With a history of previous operation on the gall bladder the possibility of a benign stricture is to be kept in mind The information regarding previous attacks of jaundice associated with pain is also important and suggests a common duct stone As carcinoma of the gall bladder and bile ducts is frequently associated with cholelithiasis which may precede the onset of a malignant process by a number of years the history of previous colic may lead to an erroneous diagnosis of stones in a case with malignancy Biliary colic may also occur in primary diseases of the liver (hepatitis cirrhosis) The character of this pseudo-colic may closely simulate that caused by a stone and is difficult to explain Perhaps it is caused by a hyper irritability and spasm of the sphincter of Oddi

Obviously the classification of jaundice into painful and painless is not of great diagnostic import While a typical biliary colic is frequent in patients with stones there are some cases in which the stone is silent On the other hand the patient with acute hepatitis may during the initial stage of the disease feel severe pain that is due to stretching of Glisson s capsule by a swollen liver The traditional picture of carcinoma of the head of the pancreas is painless jaundice but sometime in the course of the disease not a few have pain occasionally quite severe

Perhaps of more diagnostic significance than the mere absence or presence of pain are rather its severity character mode of onset and radiation The pain may be sharp and colicky or a dull heavy sensation The colicky pain usually appears suddenly rapidly reaches a maximum intensity where it may require the administration of a narcotic and is followed by a short period of spontaneous relief Pain of that character is more frequently associated with extrahepatic disease such as obstruction by stone and/or infectious processes in the biliary passages The other type of pain is usually not severe enough to require the administration of anodynes is dull heavy or stretching in chara [illegible] and more or less continuous instead of being paroxysmal I [illegible] e commonly associated with a primary disease of the liv [illegible] is acute or chronic hepatitis cirrhosis, or malignancy D [illegible] cf the gall bladder secondary to obstruction of the comm [illegible] ict by carcinoma in the head of the pancreas has somewha [illegible] haracteristics

With colicky pain, jaund [illegible] ts appearance abruptly and may become quite pronoun [illegible] to 48 hours after the onset

affection of the bile ducts in young subjects (under 15 years of age) in about *half* of which number jaundice was also present were collected from the literature The sex factor plays some role Statistically obstructive jaundice in *women is most likely to be* caused by stones while in a man the chances of a neoplastic obstruction are distinctly greater

The knowledge of occupational factors may be helpful For example a patient with Weil s disease will often give a history of exposure to surroundings where there are stagnant collections of water contaminated by infected rats (sewer workers)

A history of a systemic disease or of *exposure to a hepatotoxic* agent usually points to hepatitis unless unmistakable evidence of obstruction is obtained However even in patients with a history such as this a primary obstructive factor may be the cause of icterus In such instances errors are not uncommon A history of exposure to hepatotoxic drugs either by injection or by ingestion is very important Arsphenamine and cinchophen are the two most frequently *encountered agents When a patient has taken antiluetic* drugs he may withhold such history thus making the solution of the problem more difficult

Jaundice in a rheumatic patient should give rise to suspicion of poisoning with cinchophen and related compounds The danger arises not only from ingestion of cinchophen under the directive of a physician but also and probably more so from self medication *with patent preparations There is a host* of antirheumatic remedies containing toxic quinoline radicals and dispensed under various trade names by druggists While it is true that only very few individuals are adversely affected by these drugs in a susceptible person the ingestion of only a very small amount may bring about disastrous results Acute hepatitis caused by cinchophen poisoning is an extremely serious disease with high mortality In case of survival *cirrhosis with ascites may be the late complications of a* pathological process progressing over a period of time The patient is both ignorant of the dangers involved by the ingestion of the drug and the symptoms (jaundice) arising from it In fact he may even *welcome* the onset of icterus for it brings partial relief of arthritic pain He at first is lulled into a sense of false security and often *seeks* medical attention too late

ciated with itching is more likely in primary liver involvement than obstruction

Marked loss of weight is a rather late manifestation of malignant jaundice and is also encountered in patients who have chronic hepatitis (cirrhosis) The emaciation evident over the upper trunk and particularly the upper extremities belies the statement about stationary or even increasing weight of a cirrhotic patient with ascites A complaint of extreme muscular weakness is rather characteristic of parenchymatous jaundice Asthenia bears no relation to anorexia and weight loss and even patients with malignancy do not complain of the intense muscular weakness that characterizes severe liver damage

After a complete and thorough history has been obtained the next step is a painstaking physical examination which is begun with inspection

The inspection should be carried out preferably in direct day light as with artificial illumination light grades of icterus may be overlooked Jaundice is first noticeable in the sclerae The yellowish tint of subconjunctival fat may be misleading but on closer inspection the distinction between the two is not difficult Some clinicians stress the diagnostic value of the different shades of color of the skin in jaundiced patients A number of various colors are mentioned but it is doubtful that all of them really have a diagnostic significance There are however three types of skin discoloration that can prove to be of at least limited value in distinguishing between the different types of jaundice Thus the skin has a lemon yellow hue in hemolytic icterus is orange or butter yellow in parenchymatous jaundice and is greenish bronze in obstructive jaundice particularly in the malignant variety The greenish tinge is due to biliverdin

Evaluation of the intensity of jaundice is only of limited differential value and the clinical estimation of intensity of jaundice by mere observation of the depth of color of the skin is not particularly reliable The discrepancy between clinical estimation of the intensity of jaundice and quantitative estimates of bile pigment in the body fluids is dependent on two factors (1) biliverdin does not react with the diazo reagent (2) the pigment once it has infiltrated the skin tends to remain there in high concentration longer than in the blood stream

of the initial attack When icterus develops painlessly, or is associated with rather vague abdominal discomfort or a dull heavy sensation the discoloration is insidious The patient himself may not be aware of it until someone calls his attention to the fact that the whites of his eyes or the skin of his face have turned yellow Because shaving is usually done either early in the morning or at night with artificial illumination, the patient seldom discovers the condition himself Light degrees of jaundice may be easily overlooked even by an experienced observer, unless the inspection is done in direct daylight

In summary it may be said that the development of icterus following a sudden attack of colicky pain points to disease of the extrahepatic biliary passages with calculus or/and infection A slowly developing jaundice without any pain at the onset or with only aching dull pain accompanied by gradual intensification of the color commonly occurs either in the case of primary liver disease or neoplastic obstruction of the extrahepatic bile ducts The pain threshold varies markedly with different individuals and what one person may feel as only slight or moderate discomfort in another person may register as intense pain This distinct variation in individual perception of intensity of different stimuli must be appraised as much as possible when the patient presents himself for examination

It is important to elicit information regarding chills With a common duct stone they are characteristically intermittent and recurrent and there may be classical Charcot intermittent fever due to ball valve calculus in the ductus choledochus Chills and fever are also encountered in pylephlebitic liver abscess and suppurative cholangitis but these symptoms are not prominent in hepatitis and if they do occur they do so early in the disease and in the pre icteric stage

The complaint relative to pruritis is hardly ever encountered in patients with hemolytic icterus but apart from this condition this symptom ceases to be of any value in the differential diagnosis for it occurs with great enough frequency in both obstructive and parenchymatous jaundice True, severe pruritis may be come common in certain types of obstructive jaundice (malignant) than in diseases of the liver, so that intense and persistent icterus not asso-

to escape detection without magnification or so large as to command instant notice It may be elevated above the adjacent skin surface and reveal visible or palpable pulsations Arterial blood flows through these angiomas centrifugally from the punctum towards the perimeter The arterial nature of the blood is verified by the use of infra red photographs in which the structure red from its content of arterial blood is lost to view Curiously enough the lesions are commonly observed over the parts of the body drained by the superior vena cava being most abundant over the face and neck Rarely they can be seen over the lower trunk and lower extremities The reason for this distribution is not known The patient may suddenly blossom out with spider nevi while under observation In some cases of diffuse liver damage they are relatively numerous but may fade and disappear with clinical improvement. Thus they wax and wane in relation to the clinical progress of the disease Spider angiomas are not to be confused with hereditary hemorrhagic telangiectasia In the latter condition the familial nature of the disorder the tendency to bleed and certain anatomical characteristics of the lesion distinguish it from cutaneous arterial spider Spider nevi bleed very rarely In an occasional patient with cirrhosis epistaxis or bleeding from the gastro-intestinal tract may be accounted for on the basis of a hemorrhage from spider angiomas of the mucous membranes

An indication of the widespread alteration in cutaneous vessels associated with spiders is the paper money skin many vessels being visible in regions of the skin where they are not seen normally Vascularization of the external aspect of the nose is a phenomenon of the same order Other alterations of cutaneous vessels include palmar and planter erythema (liver palms')

The evidence of collateral circulation with distended cutaneous veins over the abdomen particularly in association with the typical appearance of caput medusae points to the diagnosis of cirrhosis with portal obstruction The abdomen should be inspected also for postoperative scars and for evidence of previous fistulous tracts

It is a curious phenomenon that with rare exceptions it is unusual for patients with cirrhosis of the liver to be hirsutive I have never seen a patient with an abundant crop of hair on his chest

It is important to note the state of nutrition of the patient In hemolytic icterus he is usually well nourished occasionally slightly

The intensity of jaundice is *chiefly dependent on the degree of* biliary *obstruction* whether the interference with the free flow of *bile be in the intrahepatic filter or in the extrahepatic* biliary system A rather striking difference in the degree of *biliary obstruction can be noted in* cancerous as contrasted with calculous or parenchymatous jaundice This is probably because of the difference *between the progressively* stenosing *or compressing effect of neoplastic* disease and the constantly dilating effect of a common *duct stone*

The sudden onset of marked jaundice *often occurs in extensive* primary *liver* damage In these cases, bilirubinemia fluctuates within a range of an intense grade of icterus, even in the presence of patency of the bile ducts However, a wide *range in intensity of* jaundice is encountered in liver disease Deep constant jaundice is usually observed in acute liver atrophy or malignant obstruction *Jaundice is absent* or slight in the majority of cases of metastatic cancer of the liver It is rather mild in hemolytic icterus, whereas with a common duct stone it is of variable degree, fluctuating within a *rather* low range of intensity Low grade and variable bilirubinemia is commonly associated with a benign obstructive lesion such as a stone, and with more chronic forms of parenchymal disease In cirrhosis, jaundice is not a prominent feature, and when it does occur it is usually late and not very intense

Factitious dermatitis, caused by extensive scratching meant to relieve pruritis, is found in hepatocellular and obstructive jaundice, but never in hemolytic icterus

Pigmentation of the skin due to deposits of melanin pigment is suggestive of chronic hepatitis (cirrhosis) It is especially noticeable in the palm creases and axillae

Spider nevi or angiomas are not pathognomonic of cirrhosis but are frequently observed in this disease (they are also seen in pregnancy vitamin-deficiency states, and in normal individuals) In hepatic disease they may be caused by the failure of the liver *to* inactivate androgenic hormones and 17 ketosteroids From a distance they have the appearance of tiny red papules and on *closer* inspection, or under a magnifying glass are seen to consist of the central point or eminence, branching legs or spokes, and an erythematous region encompassing these structures and often extending beyond the radius of the legs The central point may be so *small as*

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may also be a small well localized area of tenderness
ıt costo vertebral angle or ın the eleventh ıntercostal
lateral border of the erector spınae muscle This may
he apposıtıon of the non perıtonealızed lıver to the pos
mınal wall ın thıs regıon

r may be enlarged ın cases of hepatıtıs or obstructıve
rom whatever cause In chronıc hepatıtıs or when en
ıs secondary to bılıary engorgement caused by a stone or
the lıver ıs usually smooth and non tender In order to
ıe lıver edge the patıent may have to take a deep breath
palpatıng hand dıps ınto the abdomınal wall thıs en
examıner to feel the edge as ıt slıps under hıs fingers
lpatıon ın some cases may be more satısfactory sınce the
ıth a tender lıver ıs apt to stop ınspırıng as the edge meets
ıner s hand The locatıon of the normal lıver edge durıng
ıratıon ıs varıable and may often be felt one fingerbreadth
costal margın When the edge ıs not definıtely palpable,
resort to percussıon for determınatıon of lıver sıze, thıs
tes the extent of the area of hepatıc dullness

r edge may be tender ın acute hepatıtıs A non palpable
(wıth dımınutıon ın the area of hepatıc dullness as de-
y percussıon) suggests eıther acute lıver atrophy or a late
ge of cırrhosıs In the case of acute lıver atrophy wıth
essıon the lıver ınıtıally enlarged may shrınk ın a com
hort tıme Whıle the edge ıs smooth and regular ın
ıtıs ıt may be ındurated and ırregular ın cırrhosıs and
n the latter ınstance the examıner may also be able to
on the surface of the lıver Occasıonally, ın some forms
epatıtıs (t lıver also may present palpable
sımulatı nancy Enormous lıvers, weıghıng
ıms chıng the um cus occur only
w melanoma, oma, Hodgkın s
Rapıd nt of the organ

undernourished while in a case of common duct stone the patient may even be obese Inanition ordinarily indicates a malignancy, but *is not at all infrequently* encountered in cirrhosis in the latter instance it particularly affects the upper extremities On the other hand, even marked obesity is often seen in patients with cirrhotic livers

A peculiar musty, rather pungent odor may be detected in close proximity to the patient or it may be at times so intense as to constitute the first impression on entering his room It is referred to as foetor hepaticus and has come to be regarded as a sign of hepatic insufficiency with poor prognostic import though in milder degrees it may be encountered in patients who will recover It is particularly characteristic of acute liver atrophy but its nature is unknown In cirrhosis it is a rather late manifestation observed either in the precoma or comatose state, as a terminal affair

After inspection there should follow a thorough palpation which may give suggestive clues and occasionally even establish the diagnosis

The doctor should look carefully for palpable lymph nodes as a mild peripheral lymphadenopathy may be encountered in infectious jaundice Neither is a search for metastatic involvement of lymph nodes to be overlooked Virchow s node under the left sternomastoid muscle nodes in the subpectoral regions, around the navel, or in the rectum (rectal shelf)

Palpation of the abdomen is a difficult matter with some patients particularly on the first visit With subsequent examinations the patient may learn to relax abdominal musculature and thus facilitate the task for the examining physician Immersion of the patient in a tub of hot water or the administration of a sedative (nembutal, injected intravenously, in the dosage of 1 to 2 gr, provided there are no contra indications) may also facilitate the examination Palpation yields valuable information concerning the size and consistency of the liver spleen and gall bladder It should also include the search for other organs and masses

The tenderness in both upper quadrants of the abdomen is more common and of greater intensity in acute hepatitis or secondary liver damage arising from calculous obstruction than in malignant obstruction In some cases liver tenderness can best be elicited by fist percussion using a jarring blow over the right lower rib

the organ is not smooth but instead hard and often irregular in addition it may be tender

The spleen is frequently enlarged in parenchymatous jaundice particularly of the chronic variety (cirrhosis) but rarely so in the obstructive type of jaundice or metastatic carcinoma It is also frequently enlarged in familial hemolytic icterus and sometimes in primary carcinoma of the liver The enlargement of the spleen in the latter instance is understandable for many cases of primary hepatic carcinoma develop in old cirrhotic livers This statement should not be taken to imply that cirrhotic patients frequently develop carcinoma which is not true but merely that carcinoma is often found in association with cirrhosis Calculous jaundice alone is accompanied by splenomegaly only when the obstruction has lasted sufficiently long to result in a biliary or obstructive cirrhosis in which case there may even develop ascites and hematemesis from eosophageal varices—the two common findings in any case of cirrhosis Usually however splenomegaly implies the presence of hepatitis or familial hemolytic icterus and is an outstanding feature in the so called Banti s syndrome Hodgkin s disease leukemia and infectious mononucleosis are other conditions to be thought of any one of these affections may be associated with jaundice

The presence of ascites can be noticed on mere inspection of a distended abdomen which is not to be confused however with a protuberant abdomen of a markedly obese individual With ascites the distention is rather uniform and in the recumbent position the abdomen broadens and bulges in the flanks owing to the collection of fluid there In the upright position the abdomen protrudes markedly and the umbilicus projects outward Movable dullness on percussion and a fluctuating wave on auscultation may confirm the impression gained on mere inspection These findings however are not demonstrable until the amount of fluid in the abdominal cavity reaches certain proportions Small amounts of fluid may be easily overlooked

Ascites is a characteristic finding in chronic hepatitis but may also occur in malignant involvement of the liver In the latter case the fluid usually has a specific gravity above 1 014 and is often found to contain mucin the presence of which is of considerable diagnostic aid Rarely ascites is encountered in long standing calculous jaundice The presence of ascites thus does not wholly ex

cases However, more often than not the organ will be seen to be *enlarged on laparotomy*, although the enlargement could not be determined clinically

Once the gall bladder does becomes clinically palpable it is practically diagnostic, for it is rarely significantly enlarged in other conditions except in the case of empyema of the gall bladder In this connection Courvoisier s law is worth remembering In cases of chronic jaundice due to blocking of the common duct a contraction of the gall bladder signifies that the obstruction is due to stone a dilatation of the gall bladder—that the obstruction is due to causes other than stone This statement has been elaborated on in the following quotation *In the presence of jaundice which is painless* and progressive and associated with consistently acholic stools a dilated gall bladder palpable through the abdominal wall is almost certain to be due to malignancy of the head of the pancreas or the lower end of the common duct (Lahey) The reason for this is that cholelithiasis is associated with cholecystitis the chronically infected gall bladder becomes smaller, non-contractile, and non-distensible as a result of the progressive fibrotic reaction in its walls Another reason is that with common duct stone the obstruction is not sufficiently prolonged to cause distention On the other hand with carcinoma of the head of the pancreas the gall bladder may initially be in a perfectly normal state allowing marked distention of the organ as the obstruction grows progressively more complete The author saw one case of carcinoma of the head of the pancreas with non palpable gall bladder in which autopsy showed that the gall bladder with densely fibrotic wall had shrunk down to the size of a large olive, contracted on a small stone within its lumen Such a gall bladder cannot distend no matter how high the intrabiliary pressure rises from obstruction and how long it lasts It would be more likely to rupture than enlarge.

Complete biliary occlusion is not essential to the presence of a palpable distended gall bladder, and the *possibility of chronic* pancreatitis should be considered in the presence of incomplete biliary *obstruction and a palpable gall bladder* The non tender smooth distention of this organ in the presence of complete biliary obstruction definitely points to the diagnosis of malignant occlusion of the terminal end of the common duct In primary carcinoma of the gall bladder which sometimes may be associated with jaundice

membered that even in complete biliary obstruction there are other factors that determine the depth of color, such as the rate and manner of hemoglobin wastage and the rate of loss of bilirubin from the blood stream through excretion by the kidneys. The values appearing in the table below are rather arbitrary and include considerable overlapping.

TABLE IX

Type of Jaundice	*Intensity of Jaundice as Determined by Quantitative Estimation of Bilirubin in the Blood*
1 Hemolytic jaundice	1 Rarely over 5 mg per cent
2 Hepatogenous jaundice	2 20 mg per cent, as high as 50 mg per cent in acute severe cases
3 Common duct stone and benign stricture	3 Fluctuates within relatively low ranges, not commonly exceeding 10 mg per cent
4 Cancer of the head of the pancreas	4 Usually 10 to 20 mg per cent, not infrequently 20 to 40 mg per cent

The icterus index is likely to be above 100 in the group of cancerous jaundice although in many instances it may be between 50 and 100 and in a few even lower. Nevertheless it is true that an icterus index of above 100 may well be expected in the majority of cases of malignant obstruction. On the other hand in calculous jaundice an icterus index of above 100 is only rarely encountered. However, as already mentioned, there is enough overlapping so that sharp differentiation cannot be made on this basis alone.

The determination of the patency of the biliary passages is of paramount importance. Considerable information can be obtained from mere inspection of the stools, as the presence or absence of normal biliary color constitutes a valuable clinical sign. A colorless or acholic stool has the appearance of clay, chalk, or ashes. A chemical analysis of the feces for the derivatives of bilirubin (urobilinogen) should be used to substantiate the gross findings noted on mere inspection. In case of doubt, duodenal intubation may be used for obtaining the necessary material. In view of the importance of

clude a common duct stone as the underlying primary cause of jaundice

Given a picture of a jaundiced patient, with evidence of loss of weight in the upper extremities, an abdomen bulging from ascites and spider angiomas on his almost hairless chest, add to it the caput medusa—and you have a classical picture of cirrhosis of the liver

In the presence of ascites neither liver nor spleen may be found enlarged by the usual methods of palpation The enlargement of these organs can then be demonstrated by dipping or thrusting the palpating fingers to reach below the fluid level (*ballottement*)

Peripheral edema may accompany ascites The swelling of the lower extremities, hepatosplenomegaly dilatation of the collateral cutaneous venous channels over the abdominal wall, and gastrointestinal bleeding (hematemesis and/or tarry stools) constitute characteristic manifestations of portal hypertension as it occurs in cirrhosis Edema of the dependent portions of the body, in the absence of a demonstrable accumulation of intraperitoneal fluid or associated with only a slight degree of ascites is independent of portal hypertension and occasionally makes its appearance in the course of severe liver damage In these circumstances it is probably attributable to hypoalbuminemia, which results from impairment of protein synthesis by the liver.

Among the laboratory findings, the estimation of bilirubinemia may be of some assistance The significance of determination of the type of bilirubin present in the blood has already been discussed

Generally speaking, the icterus index is usually higher in cancerous than in calculous jaundice, but there is sufficient overlapping to prevent reliability of any arbitrary dividing level in diagnosis This caution also applies to other forms of jaundice A sudden increase in the intensity of icterus from moderate to more marked degree is suggestive of an inflammatory condition in the biliary system (cholangitis, choledochitis) The reverse suggests the same pathological processes in the period of resolution of the inflammatory lesion in the bile ducts as well as release of stagnant bile Formerly this rapid fluctuation in the intensity of icterus was thought to be incompatible with parenchymal liver disease, but the experience in the pandemic of infectious hepatitis during the last war has demonstrated the falsehood of such an assumption It should be re

matous jaundice On the other hand the stool may be normal in appearance throughout the course of even severe parenchymal liver disease because both intra and extrahepatic biliary passages are then patent The color of the stool may also fluctuate from time to time with alternation of cholic and acholic stools in cases of common duct stone corresponding with the intermittent occlusion of ductus choledochus The stool that assumes a lighter color as the jaundice progresses and finally becomes continuously acholic points to mechanical obstruction by a neoplasm there may be variations in the color of the stool at the onset of the disease but once the stools become acholic they rarely become colored again without operative intervention

For more accurate determination of the degree of oligocholia or complete acholia quantitative estimations of the amount of bile can be carried out For the technique of these tests and the detailed interpretation of the results the reader is referred to Chapter v A brief résumé will be presented here for emphasis

In complete obstruction of the common duct by carcinoma the per diem amount of the feces urobilinogen is usually less than 5 mg while the opposite extreme is observed in hemolytic icterus In the latter condition values considerably above the normal will be found particularly during hemolytic crisis In calculous obstruction or parenchymatous jaundice the urobilinogen content of the stools will be found to fluctuate within rather wide limits of very low to practically normal figures depending upon the degree of intra or extrahepatic obstruction as it varies in the course of the disease In liver disease urobilinogen seldom disappears from the feces for any consecutive four day period because a complete suppression of bile flow of this duration is relatively rare although it is known to occur in a few cases for even longer periods Intra hepatic obstruction is particularly characteristic of arsenical hepatitis but is also frequently present in other varieties of parenchymatous jaundice Such cases are difficult to differentiate from mechanical occlusion of the common duct The studies on urobilinogen excretion in the urine when correlated with the results of the liver function tests may help to prevent one from misdiagnosing them as surgical jaundice The diseased condition seems to be more severe in obstructive hepatitis than in liver disease without obstruction in the hepatic filter

this finding the presence or absence of bile in the stools should be checked repeatedly whenever the diagnosis is uncertain

An acholic stool signifies obstruction However it is important to remember that obstruction need not necessarily be determined

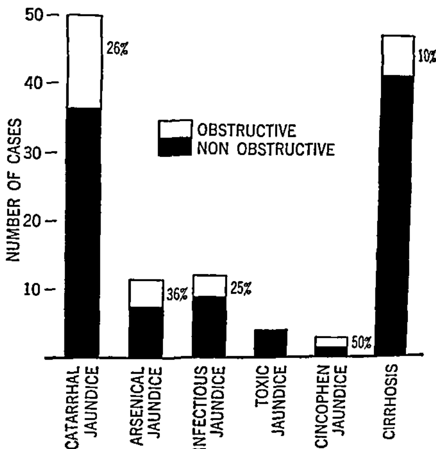


Fig. 13 Incidence of obstructive phenomenon in cases of acute hepat t s Accord ng to etiolog c group ng and in cirrhosis with jaund ce From F Steigmann and H Popper Courtesy of *Gastroenterology*

by gross occlusion of the extrahepatic biliary system intrahepatic obstruction is productive of the same results This accounts for the acholic stools in acute hepatitis although the obstructive stage of intrahepatic disease is usually of a comparatively short duration With initial stages of recovery normal color is restored Thus an intermittently acholic stool is frequently encountered in parenchy

that reabsorption of urobilinogen from the intestinal tract is faulty or that the liver even though damaged is yet capable of disposing small amounts of urobilinogen which were reabsorbed [Watson]

The determinations of daily urobilinogen excretion in the stool and urine offer the best means for establishing the presence of complete biliary obstruction This may be safely assumed to be present whenever the daily excretion of urobilinogen in the feces is less than 5 mg * Complete biliary obstruction is encountered chiefly in malignant occlusion of the extrahepatic bile ducts when it is usually persistent and may be accompanied by evidence of bleeding into the intestinal tract

The limitations of liver function tests with reference to the differential diagnosis of jaundice have already been discussed These tests are not needed for establishing the diagnosis of hemolytic icterus As to the differentiation between hepatogenous and obstructive jaundice it is worth emphasizing once more the necessity for performing these laboratory procedures early in the course of the disease and before liver injury secondary to extrahepatic occlusion has time to supervene Even when done at the optimum time there is considerable overlapping in the results obtained No single laboratory procedure can furnish a reliable diagnostic aid At best even when it is possible to do a whole array of different tests and have some of them repeated in a series great difficulties may be encountered *although valuable information can frequently be gained* Serial repeated tests are almost the only ones of value It is desirable to use at least two liver function tests one measuring the metabolic and the other the excretory function of the liver

The practical importance of a definite diagnosis in any given case of jaundice lies in the classification of patients in the medical and surgical groups for the treatment is obviously different in the two It is a part of wisdom not to hurry the diagnosis in acute cases particularly in the absence of serious infection such as abscess of the liver empyema or perforation of the gall bladder Some delay is justifiable for two reasons First considerable harm can be done by doing a laparotomy on a patient with parenchymatous-liver disease

* Very small amounts of urobilinogen are undoubtedly derived at times from the bilirubin of bile-stained epithelial cells of the colon The amount that might be derived in this way has never been determined with certainty but it is probably hardly ever greater than 5 mg a day and rarely as much as that

Thus in conjunction with clinical findings the color of the stool serves as an important diagnostic aid Generally speaking jaundice accompanied not only by pain but also by bile in the stool or in the material obtained by duodeno biliary drainage, speaks for calculous or hepatocellular jaundice, while jaundice without pain and with no bile in the stool or duodenal contents points to malignant ob struction Limitations inherent in this generalization are to be kept in mind

The *gross inspection and chemical examination of the stool* for bile may well be supplemented by an analysis of the urine for bile salts and bile pigment The qualitative tests are very simple and therefore can easily be carried out by the physician himself, without the aid of any elaborate laboratory equipment The presence of bile salts in the urine as determined by the simple foam test rules out *an uncomplicated hemolytic icterus The presence of bilirubin in* the urine as determined by any one of the uncomplicated tests which can be performed at the bedside, at once identifies regurgita tion jaundice With the simple qualitative determination of uro bilinogen in the urine, a positive result is strongly against the diag nosis of carcinoma of the extrahepatic biliary tract

In the presence of a strongly positive test, hepatocellular jaun dice is more than likely to exist, although the possibility of liver injury secondary to benign extrahepatic biliary obstruction must also be considered as for example in case of common duct stone with cholangitis In common duct stone not associated with acute biliary tract infection and not of long enough standing to involve the liver, secondary urobilinuria generally is not as marked as in primary parenchymatous liver disease However, while urobili nogenuria is much more often observed in marked degree in hepato cellular jaundice, too much overlapping occurs to permit differen tiation on this basis alone The test may also give a strongly posi tive result during crises of hemolytic icterus

The absence of urobilinogen from the urine in patients with jaundice is not safe evidence that there is complete interference with bile flow such as obtains in malignant obstruction Thus in cases of calculous jaundice with incomplete biliary occlusion or in cases of parenchyma tous jaundice accompanied by finding of at least small amounts of urobilinogen in the stool, urobilinogen, strangely enough, may be com pletely absent from the urine It can only be assumed in these cases

erroneously diagnosed as a case of surgical jaundice Secondly in case surgical intervention is indicated some time is required for preparing the patient for surgery and this same interval can be utilized for observing him and carrying out the necessary diagnostic procedures Unless one is absolutely sure of the diagnosis the best policy is to consider the case as that of liver disease until proved otherwise or until some time has elapsed without alleviation in the general condition of the patient However the period of watchful expectancy should not be unnecessarily prolonged lest irreparable liver damage develop from an obstructive lesion amenable to surgical removal

BIBLIOGRAPHY

Beau W B *Am J Med Sci* 204 251 1942

Bloomfield A L *Am J Med Sci* 195 429 1938

Boyce F F and McFetridge M H *Surgery* 4 280 1938

Heyd C G *New England J Med*, 217 161 1937

Holbrook A A *Am J Digest Dis and Nutr* 3 315 1936

Lahey F N *Surg Clin N America* 14 1127 1934

Lichtman S S *Diseases of the Liver Gallbladder and Bile Ducts* Philadelphia Lea & Febiger 1942

McMaster P S and Elman R *J Exper Med* 41 513 1925

McNee F J *Quart J Med* 16 390 1923

Meyer K A and Steinmann F *Surg Gynec & Obst* 67 640 1938

Potter A H *Surg Gynec & Obst* 66 604 1938

Snell A M *Surg Gynec & Obst* 63 596 1936

Snell A M *Canad an M A J* 37 319 1937

Watson C J *J A M A* 114 2427 1940

Watson C J *Arch Int Med* 59 206 1937

Watson C J *Illinois Med J* 86 196 1944

Williams D H and Snell A M *Arch Int Med* 62 872 1938

Yater W M *Proc Inter-State Postgraduate Med Ass of N America* 13 17 Oct 1941 p 375

TABLE X

CLINICAL DIFFERENTIATION BETWEEN THE MAIN TYPES OF JAUNDICE

	Hemolytic Jaundice	*Parenchymatous Jaundice*	*Obstructive Jaundice*	
			Benign (calculous)	*Malignant*
Familial factor	frequently present	absent	absent	absent
Age at onset	adolescence and early adulthood	*early adulthood and middle life*	*middle life*	middle life and old age
Mode of onset	insidious in more common types	fairly rapid in acute forms, more insidious in chronic forms	frequently abrupt	insidious
Principal symptoms	lassitude, decreased exercise tolerance, palpitations, rheumatic pains, symptoms may be conspicuous by their absence	malaise, frequently extreme weakness, anorexia, vomiting, diarrhea, or constipation	pain, chills, and fever (Charcot fever)	cachexia, anorexia, generally downhill course
Pain (abdominal)	abdominal crises or painless	dull aching pain or painless	acute colicky pain	painless or dull aching pain
Loss of weight	not prominent	not prominent, except in severe cases and in chronic types	*usually none*	*marked*
Hemorrhagic tendencies	absent	only in severe cases	present in long standing cases	may and may not be present
General appearance	Usually appearance of fairly good health	varies from appearance of a well person (except for icterus) to that of a desperately ill patient	usually appearance of fairly good health, *looks ill only* during acute and severe attacks	appearance of a chronically ill patient
Jaundice	lemon yellow	butter or orange-yellow	orange yellow or greenish brown	greenish brown
Spider angiomas	absent	characteristic of chronic forms	absent	absent
Liver	*may be enlarged*	enlarged, *smaller than normal* in acute atropy and terminal stage of cirrhosis	*usually normal*	*becomes enlarged later* in the disease
Spleen	enlarged in many cases	enlarged in about 25 per cent of the cases	normal	may become enlarged later in the disease

PART II

HEMOLYTIC JAUNDICE

In the group of hemolytic icterus are included a number of various conditions that all have one common denominator excessive blood destruction Although in some instances other factors play at least a contributory role in the production of jaundice, still the hemolysis of red blood corpuscles is the fundamental mechanism responsible for icterus Here we are mostly concerned with those disease entities in which hemolytic anemias are the outstanding feature Perhaps the term hemolytic is not altogether descriptive of the actual state of affairs *Although in some conditions the* process may be hemolytic in a strict sense of the word, in others the actual mode of destruction of the erythrocytes is not definitely known Therefore the term will be used more in a not too well-delineated hematologic sense rather than with its strict immunological meaning

Excessive blood destruction is often conditioned by certain morphological alterations of the red corpuscles These morphological deviations from the normal are different for the various disease entities

Classification of Hemolytic Anemias

(Modified after Wintrobe)

A Acute and Subacute Hemolytic Anemia
1 Protozoal parasites (malaria)
2 Bacteria (B Welchii streptococcus hemolyticus)
3 Chemical poisons (phenylhydrazine, sulfanilamide)
4 Animal poisons (snake venoms)
5 Vegetable poisons (favism)
6 *Naturally occurring agglutinins (mismatched transfusions)*
7 Hemolysins of the immune-body type
  a Paroxysmal (cold) hemoglobinuria
  b Acute acquired hemolytic anemia of unknown etiology (Lederer s anemia)

TABLE XI

SICKLE CELL DISEASE

Clinical Features—This is a chronic hemolytic disorder principally encountered in Negroes and characterized clinically by the symptoms of anemia rheumatoid manifestations cardiac murmurs chronic leg ulcers and abdominal crises However symptomatology is variable In some patients only icteric sclerae and pallor of the mucous membranes may betray the presence of this condition In others a history of chronic weakness lassitude and rheumatoid pains may be elicited The course of the disease is sometimes punctuated by attacks of severe abdominal pain that in some instances may be precipitated by gallstones which these patients are so prone to develop Cardiac symptoms and signs are frequently encountered Among the chief physical findings are jaundice cardiac enlargement and murmurs bony deformities and chronic leg ulcers Liver and spleen may be enlarged

Laboratory Findings—Anemia of variable degree with nucleated red blood cells and sicklemia are characteristic Other diagnostic features consist in decreased erythrocyte fragility and evidence of active hemolysis (bilirubinemia with indirect van den Bergh reaction) X ray studies may demonstrate cardiac enlargement and bony lesions (osteoporosis hair on end appearance of the skull etc.)

Differential Diagnosis—In association with cardiac findings rheumatic pains and low-grade fever the picture may be mistaken for that of acute rheumatic fever with carditis The main differential point is of course sicklemia To this may be added jaundice and evidence of excessive blood destruction The history suggestive of rheumatic fever in a Negro should arouse the suspicion of sickle-cell disease and lead to the search for sicklemia by special methods

Jaundice abdominal pain and vomiting simulate a gallstone colic. In the presence of hepatomegaly parenchymatous jaundice may be suspected The indirect type of van den Bergh reaction will aid in establishing the hemolytic nature of the disorder and thus distinguish it from hepatocellular or obstructive jaundice

a hypochromic anemia and splenomegaly The diagnosis is substantiated by the presence of target oval and stippled red cells increased hypotonic resistance of erythrocytes and complete refractoriness to iron therapy

Sickle Cell Disease This disease was first described in 1910 and is known as a hereditary and familial form of a chronic hemolytic

B Chronic Hemolytic Anemias

1 Target oval-cell syndromes (Mediterranean anemia)
2 Sickle-cell anemia
3 Familial or congenital hemolytic jaundice
4 Chronic acquired hemolytic jaundice
5 Symptomatic hemolytic jaundice (leukemia, Hodgkin's disease etc)
6 Nocturnal hemoglobinuria

Target Oval Cell Syndromes—Sickle Cell Disease

Sickle-cell anemia belongs to a most interesting group of conditions with inborn abnormalities of the red blood corpuscles which includes, in addition, chronic congenital hemolytic icterus, Cooley's disease (Mediterranean erythroblastic anemia), and ovalocytosis More specifically, sickle-cell disease can be classified with the Mediterranean *target-oval-cell syndromes, which are characterized by a* reduction in the hemoglobin level, hypochromia, abnormalities of red cells (target cells, oval cells, sickle cells,* and stippled cells) increased resistance of erythrocytes to hypotonic salt solutions and complete refractoriness to iron therapy The increased hypotonic resistance distinguishes this group from congenital chronic hemolytic icterus Individuals without anemia or evidence of other abnormality, but showing increased numbers of target, oval or sickle cells (sicklemia) are encountered A high familial incidence of this trait will almost always be found in any given instance of anemia of this type Interestingly enough there is a definite racial factor involved, the trait or the disease occurring mostly in people of Mediterranean origin (more particularly Italian), with the exception of sickling, which is most common in Negroes There is strong evidence in support of the possible relationship of the Mediterranean target-cell syndrome to the (African) sickle-cell syndrome

In a person of Mediterranean (and particularly Italian) origin the question of target cell anemia should be considered in the presence of a hemolytic type of jaundice, cardiac systolic murmurs

* Sickle cells are peculiar sickle shaped and oat shaped red blood corpuscles. Ovalocytes are elongated oval shaped or elliptical blood corpuscles resembling the normal erythrocytes of lower vertebrates and some mammals (camels) Target cells are unusually thin erythrocytes having the appearance of bull's eyes, this appearance is due to preponderance of hemoglobin in the center and periphery of the cell the hemoglobin concentration in the intermediate zone being less than usual



Color Plate 1 Sickle cell disease Elongated sickle-shaped erythrocytes typical of this condition are numerous An occasional nucleated erythrocyte is found After *Blackfan Diamond and Leister Courtesy of The Commonwealth Fund*

disorder characterized clinically by the symptoms of anemia, rheumatoid manifestations, cardiac murmurs, *chronic leg ulcers, and acute abdominal crises*. It is distinguished by the presence of the sickling trait, increased hypotonic resistance of erythrocytes (*decreased fragility*), and signs of excessive blood destruction. Large numbers of target cells may also be present. The latter *finding links it with the* Mediterranean syndromes mentioned previously. With these syndromes, sickle cell disease possesses other features *in common* (1) all gradations of the sickle cell trait, at the lower end of the scale there being individuals without anemia or evidence of other abnormality except for sicklemia, * (2) hypochromic anemia with hemolytic type of jaundice, (3) splenomegaly, (4) cardiac murmurs, (5) increased erythrocyte fragility. However, as already pointed out, the racial incidence is strikingly different. Sickle-cell disease is essentially peculiar to Negroes, although it is also encountered in white people. It seems to be more than a coincidence that among the whites this disease afflicts mostly persons *of South Italian stock*. This serves as another link in the chain of evidence pointing to the close relation between the sickle cell and Mediterranean target-oval cell syndromes. The occurrence of the sickle cell trait in Puerto Ricans and Mexicans is understandable, because of the high incidence of cross breeding with the Negro race.

Sicklemia must be distinguished from true sickle cell disease, as the sickle-cell trait alone appears to be of little clinical significance, although it is a necessary predisposing condition in the development of the disease. Under what circumstances the sickle cell trait is converted into a disease state is not known. Perhaps whenever certain factors particularly favorable for sickling are present, a sufficiently large number of cells are affected to give rise to a clinically recognizable condition. Such factors may include local or general anoxemia, infection, surgical procedures, and other circumstances known to slow the circulation of the blood.

Sickling is a property of the red cells rather than of the plasma. The assumption by the erythrocytes of the characteristic crescentic shape occurs in an atmosphere deprived of oxygen and is favored by a lowering of the pH. The process is reversible as exposure to oxygen is effective in restoring sickle cells to a circular form.

* About 7 per cent of the *Negro population* is *estimated to* exhibit sicklemia, only a very small percentage in this group have active sickle-cell anemia and other symptoms and signs of sickle cell disease.

COLOR PLATE 1 Sickle cell disease Elongated sickle shaped erythrocytes typical of this condition are numerous An occasional nucleated erythrocyte is found After Blackfan Diamond and Leister *Courtesy of The Commonwealth Fund*

Strangely enough, although in hypotonic saline solutions the sickle cells are even more resistant to destruction than are normal erythrocytes (decreased fragility), the sickle cell anemia is of a hemolytic type The sickle cells have been demonstrated to have a somewhat diminished resistance to mechanical trauma as compared with the normal cells Possibly the hemolysis is caused by the mechanical impaction of masses of deformed red blood corpuscles in the smaller blood vessels of various organs Active phagocytosis of defective erythrocytes by macrophages, with liberation of hemoglobin, has also been suggested Whatever be the mechanism of blood destruction associated with sickle cell anemia, there is ample clinical and pathological evidence available unmistakably showing that the anemia in question is of hemolytic origin * Jaundice with an indirect van den Bergh reaction in the blood serum and normal-colored stools with increased urobilinogen content testify to that effect Pathologically blood destruction is demonstrated by evidences of increased activity of the reticulo endothelial system throughout the body, showing phagocytosis and large deposits of hemosiderin in various organs

The pathologic process consists essentially of occlusive vascular phenomena produced by red-cell impaction mentioned above and by thickening of the walls of small and medium sized arteries and endarterial intimal proliferation This occurs both in association with and in the absence of intravascular thrombosis The results are ischemia necrosis, and fibrosis of the affected tissues and organs The clinical manifestations of the disease are determined by these pathological changes and the usual symptoms and signs of anemia from any cause The pathological alterations in the bones may also be accounted for by hyperplasia compensatory to the increased blood destruction with osteosclerosis as a secondary phenomenon Parenchymal lesions of the liver may occur

Anemia is only one consequence of the sickle cell trait, and probably not its most dangerous one Circulatory stasis in the small blood

* To explain the precipitation of hemolytic crises it has been postulated that sickled cells accumulate in the circulating blood between crises owing to an increased tendency of the erythrocytes to sickle as they become older The concentration of the sickled forms eventually becomes so high that they suddenly precipitate out in a more or less simultaneous capillary blockage An altered state of blood coagulability may serve as the trigger mechanism As far greater proportions of sickled cells are destroyed in the crisis than are those still normal in shape relatively few sickled forms remain in the circulation Therefore the hemolytic activity during the intervals between crises is not as marked and so remains until greater numbers of younger forms mature sufficiently to become sickled

vessels of the internal organs is the primary and the most disastrous consequence of sicklemia Sickle cell disease would therefore be a more appropriate designation for this condition All this makes it easy to understand why sickle cell disease varies so widely in clinical picture and course It also varies widely in regard to age Active and

TABLE XII

INCIDENCE OF CHOLELITHIASIS IN SICKLE CELL DISEASE

Age	*Total Number of Autopsy Cases*				*Number of Cases with Cholelithiasis*		
	Male	*Female*	*Sex Not Given*	*Total*	*Male*	*Female*	*Total*
0-10	6	6		12	1	1	2
11 20	2	6	1	9	4	1	5
21 30	8	5		13	3	2	5
31 40	3	2		5			
41 50	1	2		3			
51-60							
61 70		1		1			
Above 70		1		1			
Total	20	23	1	44	8	8	12

After Weens H S Ann Int. Med.

latent sickle-cell disease with and without anemia must be distinguished from each other

Symptomatology is variable the patient frequently may not have any symptoms for quite some time thus demonstrating remarkable adaptation to the disease state Only icteric sclerae and pallor of the mucous membranes when accidentally discovered betray the fact that there is something wrong Such state of adaptation however is not continuous and from time to time certain symptoms appear signifying relapse or else change from a latent to an active stage The patient may complain of weakness and lassitude A history of rheumatoid pains may be elicited with migrating pains in the bones joints and muscles, Sometimes a dramatic complaint is made

of severe abdominal pain which may be sharp or stabbing in character being localized to the epigastrium or either side of the abdomen With fever and leucocytosis the picture may simulate that of an acute abdomen and the patient may be erroneously subjected to a laparotomy A number of patients have been operated on for appendicitis ruptured peptic ulcer and cholecystitis

In association with jaundice and vomiting a gallstone colic may be suspected In fact the patients with sickle-cell disease are prone to develop gallstones the phenomenon being common to both sickle cell anemia and congenital hemolytic jaundice It is believed that an excess of bilirubin in the bile will favor an aseptic precipitation of pigment in the biliary tract However only relatively few abdominal crises in sickle-cell anemia can be explained solely on the basis of biliary colic Patients with sickle-cell anemia and cholelithiasis have often been known to continue suffering with abdominal pain and crises after cholecystectomy In autopsy reports biliary calculi are frequently recorded

As yet the cause of pain in the abdominal crises has not been satisfactorily explained Hepatic infarcts splenic hemorrhages nerve root pains due to vertebral changes thrombotic process or vascular engorgement with subsequent stagnation of the blood stream have been suggested Transient acute hepatomegaly associated with abdominal pains nausea anorexia fever headaches leucocytosis and hepatogenous component of jaundice added to that of hemolytic origin has also been proposed as an explanation of one type of abdominal crisis that occurs in this disease as it does in congenital hemolytic icterus

Cardiac symptoms and signs are frequently encountered Cardiac *involvement has been ascribed to thrombosis in the pulmonary* vessels which results in strain on the heart (*cor pulmonale*) In association with rheumatic pains and low-grade fever the picture may be mistaken for that of rheumatic fever with carditis The main differential point is of course sicklemia To this may be added jaundice and other evidences of blood destruction which will be mentioned later Epistaxis is a frequent complaint.

Among the chief physical findings are jaundice (icteric sclerae with a greenish tinge) heart findings such as cardiac enlargement and murmurs with accentuated second pulmonic sound and bone deformities such as kyphosis scoliosis saber shins and in some patients a tower shaped skull also seen in some cases of congenital

hemolytic icterus and Gaucher s disease Fairly characteristic are chronic leg ulcers found over the internal and external malleoli and stubbornly resisting the usual methods of treatment Liver and spleen may be enlarged The liver involvement may give a picture similar to that of catarrhal jaundice and then may be accompanied by marked increase in icterus Cerebral manifestations usually diag nosed as thrombosis or intracranial hemorrhage have been reported frequently

In some cases the roentgenogram of the chest demonstrates that the heart is enlarged to the right and to the left and the pulmonary conus may be prominent simulating the heart configuration in mitral valve lesions A rather characteristic roentgenographic appear ance of the bones is frequently noted A peculiar radial striation is observed in the skull giving it the hair on end appearance also seen in Cooley s anemia and congenital hemolytic jaundice The vertebral bodies may be flattened In the long bones osteosclerosis with cortical thickening and generally patchy irregularities in the density and pattern of the bone structure can be seen

The laboratory findings reveal an anemia of variable degree with nucleated red blood cells and increase in reticulocytes testifying to the attempts at blood regeneration by the bone marrow Frequently sickled cells cannot be seen in an ordinary smear Sicklemia how ever can be easily demonstrated when a drop of fresh unstained blood is sealed off from the air under a cover slip on a slide In a few hours marked sickling may be observed in such preparations It is important to carry out this procedure in every case of suspected sickle-cell anemia when the characteristic cells cannot be seen in significant numbers on an ordinary blood smear

The resistance of the red blood corpuscles to hypotonic saline solutions is usually increased (decreased fragility) in contrast to increased fragility in congenital hemolytic icterus

Leucocytosis which is particularly marked during hemolytic crisis is present The urine may contain albumin and casts There is an increase in bilirubin concentration in the blood and the van den Bergh reaction is characteristically of the indirect type in un complicated cases The feces contain an increased amount of uro- bilin as would be expected in the presence of increased blood destruction In patients with hepatic complications the qualitative van den Bergh reaction may change from negative direct to imme- diately positive direct indicating that in addition to bilirubin pro-



Fig. 14 Roentgenogram of the thoracic spine of a patient with sickle-cell disease showing osteoporosis

duced in excess and retained there is also present in the blood bile pigment regurgitated back into the circulation from the liver as a result of hepatic derangement During such episodes of liver in volvement there is a sharp increase in bilirubinemia and urobilin excretion in the urine and bilirubin (apparently of the direct reacting type) may also appear in the urine Liver function tests reveal impairment of hepatic function In other words there is evi dence of a hepatogenous factor added to the hemolytic type of icterus (mixed jaundice)

Sickle-cell disease is frequently overlooked and mistaken for rheumatic fever, osteomyelitis acute abdominal disease or neuro logical disorder Unless the possibility of sickle cell anemia is kept in mind and special care taken in demonstrating the abnormal cells in the blood an error in diagnosis may occur The history suggestive of rheumatic fever, with cardiac findings and anemia in a Negro should arouse the suspicion that one may be dealing with sickle cell disease and consequently should lead to the search for sicklemia by special methods

Congenital Hemolytic Jaundice (Minkowski Chauffords)

(Chronic Familial Hemolytic Jaundice Acholuric Icterus Chronic Acholuric Jaundice, Familial Splenomegalic Jaundice Spherocytic Jaundice, etc)

This is a congenital (familial) disease characterized by chronic hemolytic anemia jaundice spherocytosis reticulocytosis increased erythrocyte fragility and splenomegaly Most of the terms by which the disease is known are not satisfactory because they are not dis tinctive enough to separate this disease clearly from others with which it has certain features in common This condition however is clear-cut enough to justify a distinct and unmistakable identifica tion Most of the above listed names such as congenital or chronic familial hemolytic jaundice chronic acholuric jaundice etc are not satisfactory for the reason that chronicity congenital predisposition familial tendency and hemolytic type of anemia with acholuric jaun dice are also features of other conditions discussed here under the target-oval cell syndromes The features that distinguish clearly the disease under discussion from the ones above mentioned are two (1) spherocytosis and (2) increased fragility of the red blood cor

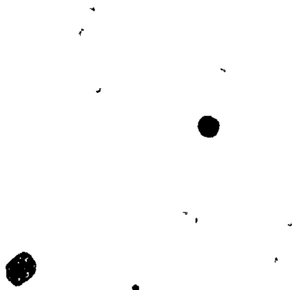
TABLE XIII

CONGENITAL HEMOLYTIC JAUNDICE
Clinical Features—This is a familial disease characterized clinically by the symptoms of anemia jaundice and splenomegaly *Symptoms vary greatly* Frequently patients are more jaundiced than sick Lassitude dyspnea palpitations and dizziness are present intermittently and may have their onset in early life. The *patient frequently states that he has been found* to be anemic or/and jaundiced in childhood or adolescence Abdominal crises similar to those described in sickle-cell disease occur in some cases Chronic leg *ulcers are also encountered Jaundice is variable and usually* is not intense The spleen is almost always enlarged in active cases
Laboratory Findings—In addition to anemia the characteristic feature in the blood smear is the occurrence of small round red corpuscles (micro spherocytes) with nucleated red blood cells and markedly increased reticulocyte count Other diagnostic features consist in increased erythrocyte fragility and evidence of active hemolysis (bilirubinemia with indirect van der Bergh reaction and increased urobilin in the stool)
Differential Diagnosis—The clinical *picture calls to mind a great variety* of disorders with jaundice splenomegaly abdominal pain and anemia The familial history and chronicity of the disease should arouse the sus*picion of some one of the syndromes in the group of hemolytic icterus* The demonstration of excessive hemolysis by means of indirect van den Bergh reaction and increased excretion of urobilin in the stool points to *the hemolytic nature of the disorder* The *discovery of spherocytosis* reticulocytosis and increased erythrocyte fragility immediately separates the case from the heterogenous group of hemolytic conditions as one of *congenital hemolytic icterus*, as in no other condition is this triad of findings seen The history of gall bladder colic elicited in some cases should not be too confusing if one remembers that these patients are prone to develop biliary calculi

patients are suffering from associated cholelithiasis In others such abdominal crises accompanied by breathlessness and lassitude may be associated with hemolytic episodes Nosebleeds are common in younger patients

The jaundice is variable and usually not intense The liver may be palpable but this is far from being a common or constant finding *The spleen is almost always enlarged in active* cases, but may not be palpable in latent cases

Chronic leg u n the region of the medial malleolus may be



COLOR PLATE 2 Congenital hemolytic anemia during crisis. Active erythropoiesis is apparent with reticulocytes making up more than half the total red cells. There are occasional nucleated erythrocytes. After Blackfan Diamond and Leister *Courtesy of The Commonwealth Fund*

the presenting complaint particularly when associated with pain They are not common but when present tend to persist for years unless cured by splenectomy

Infantilism and other endocrinological disorders are encountered and the tower shaped skull is present in some cases Other bony abnormalities present a roentgenological appearance similar to that found in sickle-cell disease

The laboratory findings reveal the presence of a moderate anemia The characteristic feature in the blood smear is the occurrence of *small round red corpuscles (microspherocytes) The demand on* the bone marrow to compensate for excessive blood destruction is evident by the appearance of nucleated red blood cells and the increase in reticulocytes The latter are markedly increased in numbers a count as high as 50 per cent or even higher may be found Hardly is there any syndrome apart from congenital hemolytic icterus in which the numbers of reticulocytes can be so strikingly increased. The resistance of red blood corpuscles to hypotonic saline solutions is decreased the point of beginning hemolysis varying between 0.5 and 0.7 per cent or higher (increased fragility) The white blood count is often within normal limits but may rise during hemolytic crises

Urine is bile free and the stools are of normal color containing an increased amount of bile pigment The serum bilirubin is increased and the van den Bergh reaction is of the indirect type (negative direct) It may however become direct positive in an occasional case with bilirubin calculi Cholecystography may frequently demonstrate stones in the gall bladder

Although the presenting clinical picture calls to mind a great variety of disorders associated with jaundice splenomegaly abdominal pain and anemia the familial history and chronicity of the disease should arouse the suspicion of some one of the syndromes in the group of hemolytic icterus Gall bladder disease in relatively young people should give rise to the same suspicion The discovery of spherocytosis reticulocytosis and increased erythrocyte fragility immediately separates the case from this heterogenous group of hemolytic disorders as one of congenital hemolytic icterus as in no other condition is this triad of findings seen

Both sickle-cell disease and congenital hemolytic icterus are characterized by a hereditary familial defect in *erythropoiesis and hemo-*

lytic crises with evidence of blood destruction and regeneration Both show some bony changes The racial predisposition is different in the two diseases Leg ulcers are more common and biliary calculi less common in sickle cell anemia than in congenital hemolytic jaundice The crucial differential points are the morphology of red cells and erythrocyte fragility spherocytes with increased fragility in congenital hemolytic icterus, and sickle cells with decreased fragility in sickle cell disease

In some patients with congenital icterus symptoms may be subclinical and so mild for many years that the first definite clinical appearance of the disorder late in life should not deter one from assuming the presence of congenital hemolytic jaundice whenever there is clear cut evidence of active blood destruction The differentiation from the various causes of splenomegaly with icterus is relatively easy, as hemolytic anemia is rare in cirrhosis of the liver, Banti s syndrome Hodgkin s disease, or leukemia

Acquired Hemolytic Jaundice

There are a number of diseases in which hemolytic anemia is present on rare occasions as a secondary and associated syndrome These are carcinomatosis, lymphosarcoma, Hodgkin s disease, leukemia severe liver disease, or dermoid cyst Following successful treatment for the underlying disorder such as removal of a dermoid cyst, all evidence of increased blood destruction frequently disappears Apart from this group of symptomatic hemolytic anemias there are cases with acquired hemolytic icterus acute and chronic In some of the acute forms a definite etiological agent can be demonstrated (favism, for example), while the others have to be called idiopathic

The acute idiopathic form is also known under the name of Lederer s anemia It is characterized by acute onset, rapid course, fever, acholuric jaundice, splenomegaly, marked anemia and leucocytosis Whenever such a clinical picture presents itself, the diagnosis of Lederer s anemia is justified in the absence of any demonstrable causative factor A history of a prodromal period of variable duration marked by increased fatigue, lassitude, and malaise may be elicited In fact the symptoms may have been developing insidiously over a period of weeks or even months making the designation of

acute rather inappropriate There is often anorexia nausea and vomiting with abdominal pain The course is febrile and pallor and jaundice are evident The hematological findings are similar to those of the congenital variety except for normal resistance of the red corpuscles to hypotonic saline solutions and rather marked leucocytosis Spherocytes may be present but there are also many macrocytes The icterus is apt to be higher than in congenital conditions, and though hemoglobinuria is occasionally present it is not characteristic of the disease

There exists a certain acute hemolytic anemia not rare in Italy, which is caused by ingestion of fava beans or by inhalation of the blossoms

The acquired chronic subacute or recurrent hemolytic icterus of undetermined etiology bears some resemblance to the congenital variety from which however it must be differentiated The most important distinguishing feature is the lack of familial history The vast majority of primary hemolytic jaundice are of the familial or congenital type However a mistaken diagnosis of the acquired type is frequently made because pains have not been taken to elicit a familial history or to study the relatives of the patient Even careful questioning of the relatives may fail to yield a history of jaundice or splenic enlargement However an assiduous hematological examination of the members of the family will reveal at least increased erythrocyte fragility in some Another distinguishing feature is the predominance of macrocytes rather than microcytes or microspherocytes in the blood from patients with the acquired type

Paroxysmal Hemoglobinurias

Paroxysmal hemoglobinuria is a condition characterized by rapid hemolysis of red corpuscles with release of their contained hemoglobin into the blood stream and its appearance usually quite sudden in the urine There are two well recognized types the so-called *paroxysmal cold hemoglobinuria and paroxysmal nocturnal hemoglobinuria* Both conditions are rather rare still the physician should have some knowledge of them as they may present problems in the differential diagnosis of jaundice The condition is also known to occur in malaria

Paroxysmal Cold Hemoglobinuria

In these patients the sudden hemolysis is due to action of autohemolysins contained in *the patient's own blood*. The hemolysins unite with the red corpuscles only at a lower temperature but the hemolytic process itself takes place after the blood is again warmed. Thus the patient coming into warmer surroundings after exposure to cold develops hemoglobinuria. Unsuspectingly he comes home and goes to bed only to find on arising the next morning that he is passing highly colored dark brownish or almost red urine. Most patients have a syphilitic infection. The outstanding symptoms are weakness, aching and pain in the back and legs, abdominal cramps, headache, malaise, chills and fever of short duration. The patient is pale, slight icterus may be present and the spleen frequently can be palpated with ease.

The history of exposure to cold may be difficult to obtain, as it may be only slight and limited to one part of the body. The diagnosis rests upon spectroscopic demonstration of hemoglobin in the urine and a test for demonstrating cold hemolysins (Donath-Landsteiner phenomenon). The procedure consists of immersing the blood sample from the patient and the control in ice water and then warming both in a water bath. In a positive test hemolysis will be found in the blood taken from the patient, whereas the supernatant serum in the control tube will be clear. In a case of acute hemolytic anemia, whether or not accompanied by hemoglobinuria, this test should be carried out to clarify the diagnosis.

Paroxysmal Nocturnal Hemoglobinuria (Marchiafava-Micheli Syndrome)

Attacks of hemoglobinuria occur chiefly during sleep. The failure of cold to activate hemolysins distinguishes this condition from that of paroxysmal cold hemoglobinuria. The fundamental abnormality in this disease resides in the red blood cells and not in the serum; the red corpuscles are abnormally sensitive to slight changes in the pH (associated with sleep?). Lowering the pH, even within the physiological range, causes increased hemolysis, whereas raising the pH reduces or entirely arrests the hemolytic process.

The clinical picture is characterized by chronic hemolytic jaundice of mild degree and hemoglobinuria following sleep, along with

splenomegaly and functional cardiac murmurs The condition may be confused with congenital hemolytic jaundice The chief differential features are the negative family history absence of spherocytes in the blood and normal erythrocyte fragility in the case of paroxysmal hemoglobinuria The final diagnosis depends upon the demonstration of hemolysis on acidification of the sample of blood taken from the patient

Familial Non Hemolytic Jaundice

This condition bears superficial resemblance to congenital hemolytic icterus in that the jaundice is of a chronic nature dates from early life and is familial but is distinguished from it by the absence of any evidence of blood destruction In other words it is a familial congenital form of icterus but without anemia spherocytosis reticulocytosis abnormal fragility of the red blood corpuscles or abnormal amounts of urobilinogen in the feces and urine

The disorder is due to a constitutional hepatic dysfunction characterized by an increased threshold of the hepatic cells to excretion of bilirubin The familial incidence of the condition its benign nature and its persistence for many years without evidence of progressive hepatic impairment indicate a physiologic or functional disturbance rather than a derangement due to well-defined organic disease It is interesting to note that this constitutional hepatic dysfunction presents a selective abnormality only in regard to bilirubin excretion and in the absence of other evidences of disturbed function of the liver While the excretion of bilirubin from the blood stream after intravenous injection of the bile pigment is definitely delayed all the other liver function tests fail to reveal any deviation from the normal Thus jaundice is of a retention type a conclusion borne out by the indirect type of van den Bergh reaction Although this condition does not belong in the group of hemolytic icterus disorders it is included here for the purpose of differential diagnosis It must be remembered that familial jaundice is not always hemolytic in type and an indirect van den Bergh reaction is not necessarily indicative of a hemolytic process

The outstanding differential features of the two diseases are tabulated below (after Dameshek and Singer)

Familial Hemolytic Jaundice	*Familial Non Hemolytic Jaundice*
Splenomegaly	Normal spleen
Spherocytosis	No spherocytosis
Reticulocytosis	No reticulocytosis
Increased erythrocyte fragility (in hypotonic saline solutions)	Normal erythrocyte fragility
Increased content of urobilinogen in the urine	Normal content of urobilinogen in the urine
Greatly increased content of urobilinogen in the feces	Normal or low content of urobilinogen in the feces
Normal result of the bilirubin excretion test	Abnormal (delayed) result of the bilirubin excretion test

The familial character of this hereditary hyperbilirubinemia is an outstanding feature The onset of the disorder becomes obvious in early life and both sexes appear to be similarly affected When symptoms do exist they are not striking and chiefly consist of complaints of lassitude and asthenia It is not clear what relation they can bear to icterus Are they perhaps neurasthenic in origin? The patient usually is able to carry on and even do heavy manual work Except for icterus the physical examination is essentially negative Liver and spleen are not palpable The condition is essentially benign for icterus apparently is not incompatible with reasonably good or even perfect health However some patients are prone to bilious attacks which may later terminate in definite cholecystic disease

The differentiation between non hemolytic jaundice and mild chronic disease of the liver (hepatitis early cirrhosis) may be difficult especially in an isolated example of the former disease Sooner or later chronic hepatitis usually shows evidence of a progressive process but at first in mild forms the blood bilirubin may give the indirect type of van den Bergh reaction The indirect variety of bilirubin is a frequent finding in the early and convalescent stages or very mild forms of hepatitis or catarrhal jaundice as the mildest disorders of the hepatic parenchyma may not be associated with regurgitation of the bile pigment into the blood stream While the bilirubin excretion test may be also positive other liver function tests may be entirely normal thus adding to the confusion The presence of bilirubin in the urine in hepatitis even mild may help to differentiate between the two conditions In the cases of more

severe hepatic disease, the differentiation of course is made easy by the presence of an enlarged liver and spleen spider telangiectasis direct van den Bergh reaction, and abnormal liver function tests

BIBLIOGRAPHY

Arena J M *J Pediat* 14 745 1939

Bauer J *Arch Surg* 4 1311 1910

Bridgers W H *Am J Path* 15 353 1939

Chauffard M A and Troisier J *Sem med*, 28 901 1908 ibid 29 601 1909

1908

1929

Med, 218 75 1938 *Medi*

19 1911

it Med 7 769 1933

th Med J 30 239 1937

Arch f Klin Med, 146

Am J Med Sci 206 158

Clin Invest, 18 637 1939.

25

1936

1 132 1915.

J A M A 101 574 1915

1930

11 1911

a Lea & Febiger 1932

PARENCHYMATOUS JAUNDICE—ACUTE AND SUBACUTE HEPATITIS

DISEASE of the hepatic parenchyma is due either to infection directly or indirectly, or to chemical agents * With regard to the etiological or exciting factors, acute hepatitis may be divided into infectious and toxic groups The former type comprises such diseases as catarrhal or epidemic hepatitis spirochetal jaundice, and yellow fever In the toxic group belong cases either secondary to chemical and vegetable hepatotoxic agents or occurring in the course of a systemic disease This differentiation is also based on certain epidemiological, clinical, and pathological factors However, the general clinical picture produced by all different types is frequently much the same no matter what the etiological agent or the details of histological changes in the liver

The onset is more or less gradual and relatively painless The prodromal symptoms may include anorexia, nausea, vomiting diarrhea, general malaise and slight fever Jaundice makes its appearance rather insidiously, and is usually not accompanied by marked pruritis At first the urine is dark and the stools are clay-colored, but as the disease progresses favorably both assume a more normal color The liver is often somewhat enlarged and tender, splenomegaly is present in about 20 per cent of the cases Examination of the urine

* Nutritional deficiencies and metabolic derangements constitute other probable causes of parenchymal liver damage in man In the course of the last few years the increased knowledge of the epidemiology and pathology of hepatic disorders has greatly modified the classic concepts with the result that the older classification of hepatitis may be discarded in favor of a more modern orientation The newer classification of diseases of the liver makes a distinction between toxipathic and *trophopathic* disorders Toxic infectious causes are responsible for the former group *whereas* the latter may be due to some dietary deficiency Thus all acute and *many chronic* forms of hepatitis belong to the group of toxipathic disorders of the liver whereas the remaining forms of chronic hepatitis and cirrhosis are to be regarded as trophopathic

reveals the presence of a variable amount of bilirubin while urobilinogen is present in normal or increased quantity The stools are acholic for only a short time in most instances The material obtained by duodeno-biliary drainage contains a moderate amount of bile (although bile may be absent for a short period) and mucous plugs The liver function tests reveal the presence of some degree of hepatic dysfunction

This is a composite picture for the entire group Variations are encountered depending on the particular type of liver disease and individual susceptibilities Thus the onset may be abrupt instead of insidious and the prodromal symptoms practically lacking The temperature may vary from that of a slightly febrile course to moderately severe pyrexia Instead of being relatively painless the jaundice may be accompanied by considerable suffering The liver may be smaller than normal instead of enlarged Certain types of acute hepatitis have distinguishing features deserving special comment and more detailed discussion such as follows these introductory remarks but *many cases cannot be pigeon holed as their cause is* not determined Often they resemble acute catarrhal jaundice clinically but the patient is ill longer

Until recently there has been no essential modification of the original concept of catarrhal jaundice as first advanced by Bamberger in 1855 and supported by Virchow in 1865 The appearance of numerous clinically similar cases in epidemic proportions among troops and civilian groups the world over brought about a reconsideration of the older concepts It led to the revision of the formerly current theory that jaundice in such cases is of an obstructive nature and is due to an initial gastro-duodenitis followed by a spread of catarrh to the epithelium of the bile ducts This gave rise to a changed nomenclature in which the term epidemic or infectious jaundice has tended to replace the older catarrhal jaundice

However the term catarrhal jaundice is too deeply rooted in the minds of the medical profession to be entirely discarded Besides there are some considerations in favor of its retention for the purpose of designating certain sporadic cases of acute hepatitis which have many features in common and aspects only too familiar to many practicing physicians

Catarrhal Jaundice

By this name is designated the most common form of acute hepatitis and in fact the commonest of all diseases with icterus encountered in clinical practice It has been known since antiquity in both sporadic and epidemic form The term implies that icterus is caused by an inflammatory 'catarrhal condition of the common duct, which obstructs the outflow of bile by the swelling of the mucous membrane of the duct and a mucous discharge forming occlusive plugs In other words, cholangitis *per se* without any pathological involvement of the liver itself was considered a determining factor in the pathogenesis of this condition A similar view was that emphasizing *the relation between gastro intestinal inflammation and jaundice* It was thought that the extension of catarrhal inflammation in the duodenum into the ostium of the common bile duct was the actual cause of icterus As a prototype of this group of cases, the patient described by Eppinger was frequently quoted This patient with catarrhal jaundice committed suicide and on necropsy a mucous plug was found occluding the ductus choledocus, the liver was not abnormal This pathological observation has not been duplicated True enough the opportunity for anatomical examination of patients with this disease rarely, if ever presents itself, as the ailment ordinarily runs a benign course terminating in recovery However, by clinical analogy with somewhat similar types of jaundice and by means of liver biopsy it became known that in many, if not most, *cases definite pathological changes in the liver do take place* Thus catarrhal jaundice is essentially just another form of liver damage

The name 'catarrhal jaundice' was coined by Virchow (1860) in the belief that a catarrhus i e a superficial inflammation with mucus formation in the duodenum, would give rise to a mucous plug in the common duct, *thus affording a mechanical* basis for the icterus However, as early as 1890 Flindt disagreed with Virchow s explanation and proposed the view that not the obstruction of the common duct but *hepatitis was the cause of so called catarrhal jaundice* Proof of Flindt s opinion was not forthcoming for a quarter of a century Special circumstances prevailing during World War I allowed Eppinger to do post mortem examinations on three patients *with catarrhal jaundice* who died of intercurrent disease (tetanus) In all three a diffuse degeneration of the liver

cells with multiple small areas of necrosis were found The intracellular biliary capillaries were seen to communicate through disrupted liver cords with the lymphatics In the following decade some clinicians advocating cholecystectomy in cases of very prolonged catarrhal jaundice with persistent vomiting, were able to perform a biopsy of the liver during the operation As a result of the histological study, diffuse hepatitis and parenchymatous degeneration, especially localized in the center of the lobule, were established as the essential lesion of the disease in question

It is possible that in some instances catarrhal jaundice begins with duodenitis extending into the common bile duct and with further propagation of the inflammatory process into the finer biliary channels In fact it may be difficult to differentiate at times between a primary cholangitis and the so-called catarrhal jaundice, although a typical case of primary cholangitis presents a clinical picture somewhat different from that of true catarrhal jaundice However the fact that the initial gastro-intestinal symptoms and the obstructive factor may both be lacking in some patients with catarrhal jaundice must be reckoned with It is also in accord with the well founded presumption that the primary disease of the liver is the underlying pathological process responsible for icterus in many cases if not in most In patients with evidence of obstruction during some phase of the disease the obstructive factor may be represented by a primary hepatic lesion associated with intrahepatic blocking an obstructive catarrhal or infectious lesion in the extrahepatic ducts or a spasm of the sphincter of Oddi Acute biliary suppression (a reflex disturbance in biliary secretion) has also been suggested as being responsible for the acholic stools in some instances

The etiology of catarrhal jaundice is not definitely known In some respects it behaves as an infectious disease, and local epidemics are not uncommon Its epidemic nature and its similarity to sporadic cases suggest an infectious origin for both Various types of organisms have been isolated from the blood of patients during epidemics of this disease among these the paratyphoid bacillus The condition is probably predominantly of virus etiology and most likely it does not represent a clinical entity but is rather composed of a group of different conditions varying with the etiological agent, the mode of origin and the site of the primary pathological process.

TABLE XIV

CATARRHAL OR INFECTIOUS JAUNDICE
Clinical Features—Catarrhal jaundice is the most prevalent form of parenchymatous jaundice Its etiology is still unknown but it is probably of virus origin It is known to occur sporadically and in mild epidemic form (epidemic jaundice) The condition is seen predominantly in young people and is the commonest type of icterus in patients who are less than thirty five years of age Jaundice appears after a prodromal period marked by gastro intestinal symptoms or symptoms simulating upper respiratory infection Icterus is often forecast by a darkening of the color of the urine increases rapidly in intensity and remains for a variable period usually three to four weeks The liver increases appreciably in size presenting a slightly tender edge The spleen becomes palpable in about 25 per cent of the cases Lymphadenopathy may be present. The stools may be clay colored for a few days to two weeks Very rapid decrease in the size of the liver accompanied by intensification of symptoms hemorrhagic phenomena lethargy or extreme restlessness have an unfavorable import and serve as a warning of the development of acute yellow atrophy
Laboratory Findings—The van den Bergh reaction is positive direct Bile salts and bilirubin are present in the urine Bilirubin is present in the stool in diminished amounts or may entirely disappear from the feces during the phase of intrahepatic obstruction Liver function tests demonstrate impairment There is a relative lymphocytosis
Differential Diagnosis—Mechanical biliary obstruction must be excluded (common duct stone malignancy) The absence of biliary colic the less rapid fluctuations in the intensity of icterus and the age of the patient are helpful in ruling out choledocholithiasis Malignant obstruction also occurs in older individuals the jaundice is persistent and there is evidence of progressively increasing obstruction (absence of bilirubin from the stools and later of urobilin from the urine) There may be blood in the stool Cirrhosis of the liver may present itself with jaundice as an initial symptom However the chronicity of this disease the presence of ascites and the development of a collateral circulation help in the differential diagnosis It is also necessary to consider the possibility of toxic hepatitis A careful inquiry should be made regarding any history of exposure to hepatoxic drugs In infectious mononucleosis the prodromal symptoms are characterized by those of acute hepatitis namely grippe like complaints anorexia nausea at times vomiting and pain or distress in the epigastric region or in the right upper quadrant of the abdomen To the fully developed clinical picture of glandular fever may be added jaundice with enlargement of the liver bile in the urine urobilinuria and impaired hepatic function The positive Paul Bunnell test and the presence in the blood smear of abnormal lymphocytes characteristic of infectious mononucleosis serve to distinguish this disease from infectious jaundice

Catarrhal jaundice is most common among younger individuals The initial or prodromal symptoms are essentially gastro-intestinal with vague abdominal discomfort anorexia nausea and occasionally vomiting and diarrhea The patient complains of malaise and is febrile at times No sooner do these symptoms disappear than jaundice with dark-colored urine and acholic stools makes its appearance In some instances jaundice is not preceded by gastro-intestinal symptoms of note or a febrile course and the patient merely feels under par with icterus serving as the first definite indication of the disease The liver is usually enlarged smooth and slightly tender The spleen may or may not be palpable

The course not uncommonly is practically afebrile throughout and is in a classical case divided into three more or less distinct phases (1) An obstructive phase associated with complete acholia and lasting on the average about 11 days There is progressive deepening of jaundice The stools are clay-colored. Urobilinogen is either entirely absent in the urine or present only in mere traces whereas bilirubin and bile salts can be demonstrated The concentration of bilirubin in the blood ranges between 3 and 9 mg per cent Leucocytosis may be observed at the onset later superseded by leucopenia (2) A critical stage of approximately four days duration characterized by a sharp decrease in the value for the serum bilirubin The stools begin to assume a more normal color Urobilin appears in the urine in increased amount owing to relief of obstruction The liver begins to recede and tenderness promptly disappears (3) A period of recovery that lasts about nine days During this period the serum bilirubin falls within the level of latent jaundice and bile disappears from the urine The various liver function tests which initially gave results indicative of hepatic dysfunction now begin to show values within the normal range On the other hand the impairment of liver function as shown by these tests may persist for a long period following clinical recovery many weeks or even months elapsing in some patients before entirely normal results can be obtained This may be interpreted as indicative of subclinical residual liver damage which in an occasional instance may continue into a phase of chronic latent hepatitis At any time in the immediate or remote future the process may flare up again with clinical evidence of disease

Frequently after the initial gastro intestinal symptoms subside and the patient believes that he has recovered he suddenly discovers that he is jaundiced and becomes alarmed *though he may* feel extremely well at this stage of the disease

Infectious or Epidemic Jaundice

To this group belong cases of icterus occurring sporadically or in epidemics The course is variable sometimes terminating in death and therefore presenting a more *serious problem than* catarrhal jaundice Spirochetal jaundice (Weil s disease) is also a form of *infectious hepatitis* However Weil s disease will be considered under a separate heading for several reasons First the causative organism (Leptospira icterohemorrhagiae) is different from that in other forms of infectious jaundice in which a virus is presumably an etiological agent in most instances Secondly the epidemiology is different in the two forms of jaundice Thirdly both the clinical course and pathological process have distinctive features in Weil s *disease Although the latter is one of the forms of infectious jaundice* not all cases of infectious jaundice are to be considered as leptospiral icterus In numerous epidemics of infectious *hepatitis* that have been investigated in only a few instances was it possible to demonstrate Leptospira as a causative organism The disease produced by the spirochete is a separate entity and must not be confused with the group of conditions known under the name of *infectious hepatitis*

The extensive literature on epidemic hepatitis that has accumulated in the past several years bears witness to *the widespread occurrence* of this disease both in the armed services and among the civilian population The newer knowledge gained during World War II has added materially to a clearer understanding of this condition particularly in regard to its etiological and epidemiological aspects

Infectious hepatitis had previously been considered a relatively *infrequent and unimportant* disease However jaundice of the epidemic type was mentioned in *De internis affectionibus,* often ascribed to Hippocrates and was recognized *as contagious* in the eighth century A D (correspondence between Pope Zacharias and St Boniface) My father in law informs me that *there was an* epi

demic of infectious jaundice in Forfarshire, Scotland, around 1900. Many patients remained ambulatory and it was not unusual to encounter them in the streets. In England several outbreaks of this disease were investigated in 1927, 1930, and 1933. In New York State 700 cases were reported in 1923. Cockayne differentiated between Weil's disease and epidemic catarrhal jaundice, of which he gave an excellent description.

During recent years, cases have been appearing in increasing numbers in both civilian populations and the armed services in various parts of the world. In fact, during the last hundred and fifty years, in almost every war an increase in the number of cases of jaundice has been observed among the military personnel. According to a report in the Bulletin of the U.S. Army Medical Department there were 22,569 cases with 161 deaths during the Civil War in a total of 2,218,559 troops. The disease also occurred in troops during the Boer War, the War of 1812, the Spanish American War and World War I. Unfortunately, before World [illegible] in [illegible] ties [illegible] work among troops in the previous campaigns [illegible], partly because facilities were more limited.

In World War II outbreaks were experienced by British troops in the Middle East in 1941 and 1942. In 1943 and 1944 similar outbreaks of an epidemic of infectious hepatitis began among American, British and French troops in the North African theater. Also a number of epidemics among the civilian population here and abroad and without any apparent connection with the outbreaks in the armed services, have been recently observed and reported. Some sporadic reports of local epidemiological significance have appeared in the literature previous to this period.

During the past few years the incidence of the disease has increased to such an extent that it has become one of the most serious medical problems. It proved to be the only pandemic disease of the last war. The reported incidence has been as high as 1 per cent of the civilian population in Norway and 4 per cent in some of the provinces. Even higher rates have been reported in certain military units in North Africa. It appears to have been widespread in Germany but, even had it been reportable, the number of cases would have remained a secret. Epidemic jaundice is reportable only

in Finland Switzerland, and the three Scandinavian countries About 65 000 cases were reported in these five countries in 1943 The case mortality has fortunately been fairly low, usually ranging from 0 1 to 1 per cent There is some evidence that it increases with age

It is now believed that many sporadic cases of icterus belong to the same group of infectious hepatitis although it has not been possible to demonstrate the etiological agent as successfully in these patients as when the disease assumes epidemic proportions With sporadic cases it is almost impossible to differentiate between catarrhal and infectious jaundice, even if such a differentiation were warranted Lichtman classifies catarrhal jaundice without pre icteric gastro intestinal upset in this group of infectious jaundice

Thus, infectious hepatitis occurs both sporadically and in epidemics In both forms it has been known to us for many years, but it is only recently that the opportunity for the study of large groups of cases has led to the awakening of interest in the disease, and the resulting clearer understanding of it

Investigations of outbreaks of infectious jaundice and experimental work on modes of transmission of the disease have established the causative factor as a filterable agent, presumably a virus The probability is that several different viruses may produce the same clinical picture Epidemic jaundice is clearly a virus disease of an extremely high degree of infectivity and capacity for covering distances, which may have some relation to the long period of incubation The agent is present in the blood and is excreted in the feces of infected persons Experimentally, hepatitis has been produced in human volunteers by parenteral injection by feeding and by nasal inoculation of material containing the infective agent With these experiments an incubation period similar to that observed in some epidemics was noted only when the material was given by the oral route Apparently this represents the natural mode of transmission, the chief source of the virus being the feces of the infected persons Anything subject to direct or indirect contamination with the excreta provides a potential means of transmission of this disease Water borne epidemics have actually been reported Nasopharyngeal droplets or secretions and urine are apparently not the common source of infection and the disease is not contracted ordinarily by direct contact However, transmission may occur by

droplet infection as well as by injection and ingestion of blood or serum In most instances the natural spread of the disease is probably by the enteric route

Since the causative agent is contained in the blood of infected persons it is only logical to expect that inoculation of the healthy with the blood or serum of infected individuals would transmit the disease That such is the case has been demonstrated experimentally on human volunteers Similar sequelae following whole blood or plasma transfusions have been reported a number of times Also the occurrence of jaundice following the use of pooled plasma and extracted whole blood and the use of improperly sterilized syringes has been described In a British institution for mental defectives 7 children received pooled convalescent measles serum and developed jaundice after 78 to 84 days Hepatitis with and without jaundice brought on by inoculation with homologous serum has received considerable prominence in medical literature during World War II following its widespread incidence as a result of inoculation of troops with normal human serum employed as a vehicle for the yellow fever virus The pathogenesis of this disease has not been definitely established However the results of considerable investigation both in this country and abroad suggest that the icterogenic agent is a virus that retains its virulence after being stored in a dried state for long periods

Infectious jaundice resulting from administration of blood transfusions and homologous serum products containing icterogenic virus has a long latency with an incubation period ranging from several weeks to a number of months as contrasted with the incubation period of approximately 7 to 30 days in the epidemic form of the disease This difference in the incubation period of the two forms of infectious hepatitis has not as yet been explained (Incubation periods of 3 to 5 weeks in spontaneous infectious jaundice 8 to 9 weeks after use of convalescent serum and 8 to 12 weeks following yellow fever immunization) Clinically the disease resulting from inoculation with homologous serum is indistinguishable from infectious or catarrhal jaundice spontaneously acquired

Thus infectious hepatitis has currently manifested itself as three clinical entities the naturally acquired condition (epidemic jaundice) homologous serum jaundice and post vaccinal (yellow fever) hepatitis There may be no fundamental difference between them

and it is possible that the clinical variations are due to the route of inoculation and to the general condition of the patient However it must be conceded that the supposed relation of the three syndromes is by no means proved *

The jaundice producing agent is present in the blood during the pre icteric and early icteric stages but disappears from the blood in about ten weeks following the disappearance of jaundice This indicates that blood donors who constitute the greatest menace are those in the pre icteric stage or with hepatitis unattended by jaundice Individuals who have recently recovered from jaundice are not accepted at Red Cross banks In view of the widespread incidence of infectious hepatitis a transient healthy carrier state may exist among some volunteer blood donors and their detection would be impossible It was prophesied that large scale use of blood and plasma transfusions would lead to the occurrence of a considerable number of cases of infectious jaundice

It seems highly probable that they may be occurring not infrequently but are not being recognized If one were not aware of the fact that jaundice may follow inoculation with homologous serum or plasma after a long latent period one would be unlikely to attach any significance to a history of transfusion three months previous to the onset of a patient s illness The real frequency of this complication of transfusion will be known only when there has been a concerted effort by physicians to recognize such cases [Beeson]

Epidemic Jaundice

The fundamental pathological change in infectious jaundice is that of hepatitis which is well pronounced by the first week after the onset and usually subsides within about four or five weeks after the appearance of icterus The essential lesions consist of the involvement of parenchymal liver cells and an inflammatory exudate in the periportal areas There are diffuse inflammation and degeneration of liver tissue during the pre icteric and icteric stages of the disease Another striking feature is presented by infiltration into the periportal and interlobular areas of polymorphonuclear leucocytes lymphocytes and plasma cells The inflammatory component

* Recent stud es have given evidence that the viral et ological agents of ep demic hepatitis and homologous serum hepatitis are not identical and differ at least in the r antigenic properties

is more marked in severe cases. The complete necrosis of the parenchyma in the periphery of the liver lobule has been observed in some instances and may cause the obstruction to the excretion of bile. In many cases there is a more or less characteristic type of degenerative lesion of the central and midzonal portions of the liver lobule. The destruction and dissociation of the hepatic cells cause rupture of the biliary canaliculi, which sometimes leads to secondary formation of biliary thrombi. Rupture of bile capillaries and biliary thrombi may produce intrahepatic biliary obstruction.

It is possible that, similar to many virus infections, infectious hepatitis represents a systemic disease with a particular affinity of the causative agent for the liver. This is evidenced in many cases by the involvement of other organs and structures such as lymph nodes, the pancreas, and the intestinal tract. It is equally possible that under such circumstances many of the symptoms attributed to the affection of the liver *per se* may be the result of the extrahepatic lesions.

The disease occurs most frequently in children and young adults (between 18 and 30 years of age).

Specific immunity is produced by a nonfatal attack of the naturally acquired disease, although it is not invariable or always lifelong. Immunity to one strain of the virus may not protect against other strains. Predisposing factors that may affect man's resistance to the infection include poor nutrition, alcoholism, unsanitary living conditions, and fatigue.

In some instances, particularly in sporadic cases, there are no prodromal symptoms of any kind. The patient first notices that the urine becomes dark and the stools light colored; then jaundice makes its appearance. More frequently there are definite prodromal symptoms preceding the onset of icterus and the disease can be divided into three stages: (1) A pre-icteric stage without jaundice and without enlargement of the liver. This is followed by (2) an acute icteric stage with enlargement and tenderness of the liver, and finally (3) the convalescent stage with a disappearance of symptoms and jaundice and a return of the liver to normal size. Acute infectious hepatitis without jaundice runs an essentially similar course.

The prodromal stage may last from only a few days to as long as two or three weeks. The onset is variable but may be abrupt with

fever, chills, malaise, lassitude generalized myalgia headache, anorexia, abdominal discomfort, and generally symptoms common to an infectious systemic disease Anorexia is often severe and striking—one is tempted to say, almost diagnostic Coryza and upper respiratory infection may be the prominent prodromal manifestations in some cases, if so, they are symptoms indistinguishable in this stage from nasopharyngitis, influenza, or early atypical pneumonia The temperature usually is relatively low and irregular, ranging between 99 and 100° F for a short period, though the disease may be ushered in by a sudden and acute febrile episode In other instances the onset may be more insidious and afebrile or practically afebrile, and is sometimes manifested by anorexia nausea later followed by vomiting extreme weakness and lassitude, vague abdominal discomfort with intestinal cramps bloating and mild distention or dull aching in the right upper quadrant or both upper quadrants of the abdomen, frequently with radiation to the back The pain is aggravated by jarring The anorexia may be most marked and in association with nausea, be the presenting symptom There may be either diarrhea or constipation The diarrhea is usually mild without any blood pus, or mucus in the stool These gastrointestinal symptoms are probably due to edema and phlegmonous changes in the stomach and small and large bowel Pruritis is not complained of at this stage of the disease, but mild arthralgia and rashes are occasionally observed In the epidemic form of the disease the acute prodromal symptoms described above sometimes last for only a few days and are followed by a relatively symptom free and afebrile interval of about one week Jaundice is then ushered in by a recurrence of fever and acute symptoms

Physical findings during the pre icteric stage are not at all noteworthy There may be some tenderness on palpation in the right upper quadrant of the abdomen The patients are not seen in this stage of the disease frequently enough to ascertain the incidence of hepatomegaly prior to the onset of icterus A helpful finding is that of peripheral lymphadenopathy usually cervical However, this sign could never actually lead to an early suspicion of the events to come except during an epidemic On the contrary, the upper respiratory symptoms with a febrile course and palpable lymph nodes may lead one to suspect some other disease entity such as infectious mononucleosis

TABLE XV

SYMPTOMS OCCURRING IN THE PRE-ICTERIC PHASE IN 200 PATIENTS WITH INFECTIOUS HEPATITIS

Symptoms	*Number of Cases*	*Per Cent of Cases*
General symptoms		
Lassitude and fatigue	137	68 5
Pruritus	93	46 5
Fever	83	41 5
Headache	53	26 5
Chills	34	17 0
Upper respiratory infection	31	15 5
Muscle and joint pains	24	12 0
Syncope	16	8 0
Epistaxis	9	4 5
Cough	8	4 0
Urticaria	6	3 0
Symptoms referable to disease of the liver or gastro-intestinal tract		
Anorexia	184	92 0
Urine dark	181	90 5
Nausea	158	79 0
Vomiting	117	58 5
Abdominal pain	114	57 0
Acholic stools	109	54 5
Constipation	45	22 5
Diarrhea	19	9 5
No pre-icteric symptoms	15	7 5

After Hoagland C L and Shank R E J.A.M.A 130 615 1946

Jaundice is sometimes ushered in by a recurrence of fever if fever has previously subsided during the prodromic stage In the absence of prodromal manifestations, the appearance of icterus *marks the onset of the disease With the development of jaundice* there may be an exacerbation of the symptoms noted in the pre icteric stage and the patient may again complain of malaise, abdominal discomfort, or/and pain and nausea, at times followed by vomiting There may also be some gas, intestinal cramps, a slight diarrhea, anorexia, and intolerance to fats The pain most com

fever, chills, malaise, lassitude, generalized myalgia headache anorexia, abdominal discomfort, and generally symptoms common to an infectious systemic disease. Anorexia is often severe and striking—one is tempted to say, almost diagnostic. Coryza and upper respiratory infection may be the prominent prodromal manifestations in some cases, if so, they are symptoms indistinguishable in this stage from nasopharyngitis, influenza, or early atypical pneumonia. The temperature usually is relatively low and irregular, ranging between 99 and 100° F for a short period, though the disease may be ushered in by a sudden and acute febrile episode. In other instances the onset may be more insidious and afebrile or practically afebrile, and is sometimes manifested by anorexia nausea later followed by vomiting extreme weakness and lassitude vague abdominal discomfort with intestinal cramps, bloating and mild distention or dull aching in the right upper quadrant or both upper quadrants of the abdomen, frequently with radiation to the back. The pain is aggravated by jarring. The anorexia may be most marked and in association with nausea, be the presenting symptom. There may be either diarrhea or constipation. The diarrhea is usually mild, without any blood, pus, or mucus in the stool. These gastrointestinal symptoms are probably due to edema and phlegmonous changes in the stomach and small and large bowel. Pruritis is not complained of at this stage of the disease, but mild arthralgia and rashes are occasionally observed. In the epidemic form of the disease the acute prodromal symptoms described above sometimes last for only a few days and are followed by a relatively symptom free and afebrile interval of about one week. Jaundice is then ushered in by a recurrence of fever and acute symptoms.

Physical findings during the pre icteric stage are not at all noteworthy. There may be some tenderness on palpation in the right upper quadrant of the abdomen. The patients are not seen in this stage of the disease frequently enough to ascertain the incidence of hepatomegaly prior to the onset of icterus. A helpful finding is that of peripheral lymphadenopathy usually cervical. However, this sign could never actually lead to an early suspicion of the events to come except during an epidemic. On the contrary, the upper respiratory symptoms with a febrile course and palpable lymph nodes may lead one to suspect some other disease entity such as infectious mononucleosis.

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After Hoagland C L and Shank R E J.A.M.A., 130 615 1946

Jaundice is sometimes ushered in by a recurrence of fever if fever has previously subsided during the prodromic stage In the absence of prodromal manifestations the appearance of icterus marks the onset of the disease With the development of jaundice there may be an exacerbation of the symptoms noted in the pre icteric stage and the patient may again complain of malaise, abdominal discomfort or/and pain and nausea at times followed by vomiting There may also be some gas, intestinal cramps, a slight diarrhea anorexia and intolerance to fats The pain most com

monly is a dull ache but occasionally becomes sharp and cutting with radiation to the back and/or the right shoulder The pain may be so severe as to simulate a gallstone colic and can be experienced not only in the region of the liver but in both upper quadrants of the abdomen On the other hand the initial prodromal symptoms may continue unabated into the icteric stage Still another variation is the clinical course as observed in instances where the symptoms

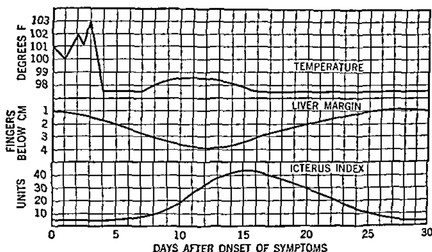


FIG 15 Schematic representation of the course of a typical case of acute hepatitis with jaundice From M H Barker R Capps F W Allen Courtesy of *J A M A*

described above practically disappear by the time jaundice sets in and are absent for the remainder of the disease process The clinical appearance of the patient may vary from that of a person hardly ill at all (apart from intense jaundice) to that of a seriously ill patient

Icterus mounts quickly to a peak in a few days to a week or two and may persist for only two to four weeks or as long as several months Here it may be appropriate to mention that the older dictum regarding *the duration of icterus as an aid in the differential diagnosis of jaundice has not been borne out* by the experience gained through more recent observation of the cases of infectious hepatitis While previously it was maintained dogmatically that jaundice lasting over a period of six weeks signified extrahepatic obstruction *usually malignant* we now know that patients with acute hepatitis at the onset may remain icteric for longer periods of time There is no apparent correlation between the intensity

of jaundice and its persistence Profound icterus may resolve quickly and milder icterus persist for weeks The icteric index may both rise and fall rather abruptly The patient often has clay colored stools for a short period Marked pruritis is unusual

During the icteric stage the most prominent physical finding is a tender enlarged but smooth liver In a certain percentage of cases perhaps as high as 20 to 25 per cent there is an associated splenomegaly The latter finding perhaps is of lower incidence in infectious hepatitis resulting from blood or serum transfusions than in the disease acquired spontaneously Ascites and peripheral edema may develop in severe cases (malignant hepatitis)

A helpful differential feature is the presence of peripheral lymphadenopathy which occurs in a good many patients This find ing is not usually observed in obstructive jaundice apart from ex ceptional cases where the obstructive factor is a part of a lymph granulomatous process such as Hodgkin s disease or leukemia

Conjunctival injection varying from mild to moderately severe has been reported in some patients This is of interest in view of its reputed importance in the diagnosis of Weil s disease Cutaneous lesions are rare but have been encountered A diffuse macular erythematous rash has been observed mostly in the pre icteric stage

In some cases in addition to bradycardia and hypotension there may be present electrocardiographic evidence of conduction dis turbances such as partial heart block This is another manifestation of the systemic nature of the disease process

With the beginning of convalescence jaundice gradually sub sides the patient becomes more comfortable or entirely symptom free the abdominal tenderness disappears promptly and the liver quickly diminishes in size In some instances the decrease in the size of the liver does not parallel the subsidence of tenderness and the enlargement may persist for from one to many months More will be said about the significance of this feature later

The laboratory findings vary with the stage of the disease and in the prodromal period there are no really diagnostic tests available although some may allow a presumptive diagnosis The most valu able laboratory procedure is the determination of bilirubinuria This can be done with any one of the very simple techniques A posi tive result presents the earliest diagnostic sign of the impending icteric stage

TABLE XVI

COMMON PHYSICAL FINDINGS IN 200 PATIENTS WITH INFECTIOUS HEPATITIS

	Number of Cases	*Per Cent of Cases*
Hepatomegaly	102	51 0
Hepatic tenderness	76	38 0
Splenomegaly	27	13 5
Hypotension (systolic pressure less than 110 mm of mercury)	38	19 0
Bradycardia (heart rate less than 60 per minute)	50	25 0
Acneform skin lesions	11	5 5
Furunculosis	3	1 5

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During the icteric stage there is bilirubinemia and an elevated icterus index The degree of bilirubinemia is variable and frequently quite marked An amazingly high icterus index of over 500 has been reported The van den Bergh reaction is of the direct type as in obstruction jaundice, even though bile may be present in the stools Hepatic dysfunction is evidenced by the results of the liver function tests The cholesterol cephalin flocculation is usually positive It is the most sensitive test, becomes positive early and frequently is the last to return to normal The ester cholesterol fraction is not infrequently below the normal range and may be exceedingly low in severe cases There is often observed a depression in the serum albumin fraction with reversal of the normal albumin/globulin ratio and concurrent elevation of the serum globulin The colloidal gold test is usually positive The alkaline phosphatase values may be somewhat elevated Particularly in severe cases there may be prolonged coagulation time and diminished concentration of prothrombin in the blood *

A mild leucopenia with relative lymphocytosis is often present at times associated with the appearance of atypical lymphocytes simi

* In some cases of infectious jaundice a striking degree of dissociation in the evidence of hepatic impairment is found For example cephalin cholesterol flocculation test may be negative and the blood alkaline phosphatase and total cholesterol high thus suggesting an extrahepatic biliary obstruction At the same time however the high concentration of urinary urobilinogen and the low percentage of cholesterol esters will point to the correct diagnosis of parenchymal liver involvement This again illustrates the need for performance of multiple liver function tests in doubtful cases and the danger of relying on only one or two laboratory procedures

lar to those of infectious mononucleosis Occasionally a slight leucocytosis is seen but leucopenia or a normal white blood-cell count is considered to be more characteristic of the disease The sedimentation rate may be slightly elevated but surprisingly enough remains normal in the very ill patients

The significant findings in the urine are in regard to bile and bile pigment derivatives While urobilinogen may be absent from the urine for a few days during the period of rising icterus which is marked by a *short stage of intrahepatic obstruction* it may later

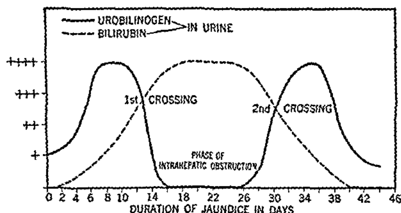


FIG 16 Schematic curve of the results of qualitative analysis for bilirubin and urobilinogen in a typical case of parenchymatous jaundice with intrahepatic obstruction From F Steigmann H Popper and K A Meyer Courtesy of *J A M A*

appear in abnormal amounts Bilirubin whose presence in the urine may be detected even in the pre icteric stage is found in increasing amounts as the jaundice deepens Albuminuria and cylindruria are frequently present

Water balance is disturbed There is a tendency to retention of fluid with increase in the circulating blood volume and interstitial fluid This is well demonstrated by water tolerance test While a normal individual excretes the ingested liter of water within the four hour period in the presence of liver damage there is considerable water retention so that 500 cc or less are excreted during the test period Some believe this phenomenon is due to incomplete inactivation of the antidiuretic principle by a damaged liver

To rule out Weil's disease dark field examinations on the blood for leptospiras should be carried out Leptospiral jaundice presents a picture characterized by more severe headache, more marked

muscle pain and tenderness, and a higher and more persistent fever Hemorrhagic tendencies and marked albuminuria and azotemia occur more commonly in Weil's disease A history of close contact with rats often gives a clue, but final diagnosis of course rests on laboratory findings

Some of the clinical features suggestive of glandular fever, such as lymphadenopathy, splenomegaly, and lymphocytosis, call for the performance of heterophile agglutination tests (some cases of infectious mononucleosis are associated with jaundice)

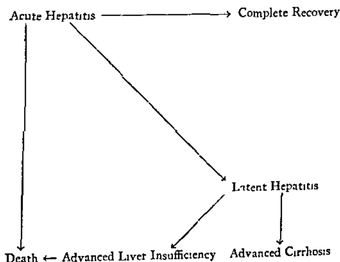
Variations in the clinical course of hepatitis bear resemblance to the variable course observed in the case of Bright's disease Acute hepatitis may be considered analogous to the acute forms of nephritis, while the chronic variety resembles the condition of the contracted kidney 'As is the case in renal disease transitions from the acute to the chronic form are noted while the pathologic changes and the degree of functional impairment are not necessarily parallel'

Acute hepatitis may progress either to death or to complete recovery But the recovery may be only apparent, the process becoming latent The latent stage may or may not be punctuated by remissions, with eventual transition to advanced cirrhosis Or the process may remain *latent until liver insufficiency is advanced*

It is important to realize that acute infectious hepatitis may oc

TABLE XVII

VARIATIONS IN THE COURSE OF HEPATITIS



cur in the absence of jaundice In all other respects the clinical picture is the same except that the disease is likely to run a milder and shorter course

The experience of recent years and particularly the knowledge gained in World War II have taught us that the disappearance of jaundice and the restoration of well being do not necessarily signal the end of a disease process Relapses are not infrequent particularly in patients who develop an intercurrent infection of the respiratory tract or who return too early to their daily routine The severity of the relapse seems to parallel to a certain extent the severity of the respiratory infection or the degree of activity resumed by the patient who believes himself or is believed by his physician to have recovered

A recurrence is marked by the reappearance of symptoms enlarged and tender liver and occasionally even jaundice Along with this there is laboratory evidence of liver dysfunction By subjecting a patient to graduated exercises following an apparent recovery, a final criterion of actual recovery can be established and used for the purpose of determining the time when the patient can be allowed to return to his daily routine The rapid fall in the icterus index and the apparent rapid clinical improvement may be misleading By repeating liver function tests and carefully watching the patient during the period of convalescence residual hepatic damage can be estimated and appropriate measures then instituted It is important to realize that hepatitis is not cured when the clinical jaundice or even the icterus index return to normal and the patient begins to feel well As indicated in the chart above some of the patients even in spite of judicious treatment, may never completely recover and rather develop latent or chronic hepatitis Others also in spite of early and well planned treatment die in the acute stage In these cases jaundice continues to increase rapidly or persists at high levels and the picture of acute liver failure develops Fortunately the patients in this group constitute a very small percentage of cases

The disease tends to be more severe when there is a past history of infectious hepatitis exposure to hepatotoxic agents such as carbon tetrachloride chronic alcoholism and with advanced age Hemorrhagic phenomena and a markedly prolonged prothrombin time that fails to respond to vitamin K are serious signs So is coma although recovery may occur even after coma has developed Mani

festations indicating a severe and approaching fatal condition are as follows (after Wilenski)

1 Severe general symptoms especially fever and chills (least im portant)
2 Anorexia or vomiting beyond the temporary or mild forms observed in the early stages of extrahepatic lesions of the biliary tract
3 Shrinkage of liver (below normal size)
4 Increasing jaundice
5 Any tendency to hemorrhage
6 Diminution of the secretion of urine not accounted for by a cor responding diminution in the intake of fluid and with or without laboratory evidence of diminished renal function
7 Demonstration of leucine and tyrosine in the urine
8 Retention of nitrogen in the blood
9 Signs of disturbed cerebral function—convulsions stupor and coma *These are evidences of impending or established hepatic cholemia* or of hepatorenal intoxication

In general fatal cases fall into two groups those that have an acute massive liver cell necrosis and die within about a week of onset and those that have a severe persistent infection over a period *as long as two months Intercurrent infection or lack of proper treat* ment appear to be the factors interfering with recovery in the latter group Some of the patients with fatal outcome die from acute liver atrophy

Acute Liver Atrophy First described as acute yellow atrophy the condition later became known also as acute red atrophy which is recognized as a later stage of the same process This pathological *entity is also known under the term of acute necrosis* a designation more satisfactory because one specific color in the pathological specimen of the liver is not *constantly observed*

It is believed by some students of liver disease that the definition of acute atrophy is not dependent so much upon the duration of clinical jaundice as the nature of the pathological process Thus the acute stage of this disease cannot be defined in terms of the period of symptoms but rather in terms of pathological findings This does not imply that a correct clinical diagnosis cannot be made or that it can only be *established* by an anatomical examination of the liver Rigid clinical criteria have been adopted for the defi nition of this condition These rest upon *the estimation of the*

amino-acid and urea content of the blood and the tyrosine content of the urine It is maintained that many forms of hepatitis and cholemia may simulate the clinical picture of acute diffuse liver necrosis but they lack these criteria It is pointed out that in many instances when the patient dies in coma after a brief spell of intense jaundice the pathological findings have revealed a subacute or even chronic process instead of an expected acute diffuse necrosis Although the laboratory data in these cases appear clinically identical with those of acute atrophy the process in question is rather that of a subacute or chronic nature

The condition is characterized by acute diffuse necrosis of the liver With cellular necrosis there is complete disorganization of structure leaving behind cellular detritus and debris Before this stage of cellular debris is reached the liver is yellow in color (acute yellow atrophy) Later when the necrotic liver parenchyma has been completely removed leaving the vascular structure of the liver lobule the organ assumes a red color (acute red atrophy) The patient may die in either stage of the disease

The clinical picture presents an intensification of the same symptoms observed in patients with catarrhal or infectious jaundice who have been fortunate enough to have a more limited and not as destructive process as the unfortunate few in whom the disease assumes the proportions and intensity of acute diffuse necrosis Anorexia and muscular weakness and prostration are extreme Jaundice is usually intense although fluctuations in intensity are observed Pain in the hepatic region or in the flanks may be quite severe At times it is colicky simulating gallstones Skin rashes are sometimes seen and hemorrhagic tendencies are universally present Hemorrhages occur into the skin mucous membranes and gastro intestinal tract with hematemesis and melena The characteristic fetor hepaticus may be noted and fever is constantly present The characteristic physical finding is the progressive decrease in liver size as determined by percussion The determination of liver size by percussion may be rendered difficult by extreme meteorism Although ascitic fluid is usually found on post mortem examination its demonstration during life is difficult Swelling of the face and dependent edema are sometimes observed Eventually drowsiness merging into coma supervene

TABLE XVIII

ACUTE LIVER ATROPHY
Clinical Features—The condition is characterized by acute diffuse necrosis of the liver and may occur under the influence of a large number of agents (infectious agent of catarrhal or epidemic jaundice hepatotoxic agents such as arsphenamine etc) The patient who was at first suspected of having ordinary benign catarrhal jaundice may become progressively worse and die with all the clinical manifestations of acute yellow atrophy The most significant features consist in intensification of all previous symptoms and icterus with marked nervous and mental disturbances and hemorrhagic tendencies Icterus progresses to an extreme degree quite rapidly while the liver decreases in size
Laboratory Findings—The most significant findings are marked bilirubinemia with direct positive van den Bergh reaction a very low range for ester cholesterol fraction in the blood an increase in blood amino acid nitrogen content hypoproteinemia marked hypoprothrombinemia that fails to respond to vitamin K therapy and the presence of large amounts of leucine and tyrosine crystals in the urine
Differential Diagnosis—The early stages of the disease may resemble catarrhal or infectious jaundice of greater than average severity However the general course of the disease and the marked increase in severity of symptoms point to the diagnosis of acute atrophy as time goes on From the terminal stage of portal cirrhosis acute liver necrosis can be differentiated by the absence of splenomegaly ascites and evidence of collateral circulation present in the former Generally speaking recognition of the typical case of acute liver atrophy presents very few difficulties when intensity of jaundice nervous and mental disturbances of a marked degree hemorrhages decrease in liver size azotemia and tyrosinuria definitely indicate the extreme seriousness of the fulminating and malignant process

Among the significant laboratory findings are marked bilirubinemia with a positive direct van den Bergh reaction a very low range for ester cholesterol fraction in the blood an increase in the amino acid nitrogen content of the blood hypoproteinemia marked hypoprothrombinemia that fails to respond to vitamin K therapy occasionally occult or gross blood in the stools, sometimes albuminuria and significantly the presence of large amounts of leucine and tyrosine crystals in the urine In no other disease is tyrosine present in the urine consistently in such large concentrations

It is now well established that an intimate relation exists between catarrhal jaundice or infectious hepatitis and acute liver atrophy It is quite probable that yellow or red acute atrophy represents an extreme end of a scale of lesions on which there are many gradations from the usual slight and readily reparable injury, such as occurs in an average case to the extensive destruction of tissue in the patient who succumbs Ordinary catarrhal jaundice may be regarded as yellow atrophy *en miniature* However, from the standpoint of pathogenesis and etiology neither term represents a single disease In other words acute liver atrophy is not an etiological entity The infectious factor is not the sole causative agent other factors quite possibly being productive of an identical end result Hepatotoxic chemicals (such as arsphenamine tetrachlorethane, and trinitrotoluene) and vegetable poisons (mushrooms) also are known to cause this condition In fact a multiplicity of etiological agents may be operative in any case Among other precipitating factors syphilis and pregnancy may be mentioned They will all be considered in detail in the discussion on toxic hepatitis It is to be emphasized here that acute liver atrophy is not a disease entity *

Subacute Liver Atrophy If the initial injury caused by the infectious and toxic agents mentioned above does not produce diffuse and acute liver necrosis the disease assumes a subacute course and is then known as subacute liver atrophy Perhaps the dose of the offending factor and the resistance of the liver parenchyma determine the extent and tempo of the pathological process Thus the difference between acute and subacute types is chiefly one of degree In the subacute process widespread initial necrosis is followed by more or less marked regenerative changes

Clinically subacute liver atrophy presents a slower course and a greater prospect of recovery Fatalities however do occur On purely clinical grounds this condition may be suspected in any case of catarrhal or infectious jaundice when the icterus fails to subside in two or three weeks An obstructive phase simulating extrahepatic biliary obstruction may be present for a limited period This stage is marked by intensification of jaundice and acholic stools but ascites is not usually found The liver function tests are positive

* The pathological findings in acute liver atrophy vary with etiological factors There is evidence of slow cell death in cases due to chemical poisons or bacterial toxins In acute atrophy of epidemic hepatitis cell destruction occurs rapidly and cell debris is removed swiftly Rapidity and completeness of destruction is believed to be a distinguishing feature of epidemic hepatitis

Homologous Serum Jaundice

A reference has been made elsewhere in regard to the fact that post transfusion hepatitis is clinically indistinguishable from common acute infectious jaundice acquired spontaneously In a patient presenting a picture of catarrhal jaundice, only the history of previous administration of whole blood or blood products can lead to a presumptive diagnosis of homologous serum jaundice Very small amounts of serum containing the icterogenic agent may transmit the disease The mortality is higher than in spontaneously acquired type

COMPARATIVE DATA ON EPIDEMIC JAUNDICE AND NOMOLOGOUS SERUM JAUNDICE

Clinical and Epidemiologic Data	*Epidemic Jaundice*	*Serum Jaundice*
History of blood and plasma transfusions	no significance	positive
Incubation period	2 5 weeks	8 16 weeks
Age distribution	most commonly under 35	at any age
Spread by contact	*not uncommon*	non-existent
Vehicle for transmission of causative agent	feces and blood	blood
Fever	*afebrile or 99° to 101° F, occasionally higher*	*seldom exceeds 100° F*
Course of the disease	usually benign, occasionally malignant	more frequently malignant

Post Vaccinal Jaundice

An epidemic of jaundice developed during World War II among troops in the United States and abroad *following vaccination* for yellow fever In the course of extensive studies it was conclusively *demonstrated that the* outbreaks were not yellow fever or modified yellow fever, Weil s disease, or any other type of leptospiral infection, any type of bacterial *infection or infectious* mononucleosis

The assumption remains that certain lots of vaccine administered for the purpose of inoculation against yellow fever carried an ictero genic agent in their component of human serum This makes the post vaccinal jaundice closely related in its etiological and epi demiological aspects to cases of jaundice developing as a result of transfusion with blood or serum As soon as it was recognized that the epidemic of post vaccinal jaundice was due to an agent pres ent as a contaminant in particular lots of vaccine and not to the virus of yellow fever used in its preparation the manufacturing method was changed and the epidemic of associated jaundice disap peared While a great number of cases developed the mortality was slight The unfortunate complication incidental to the use of several contaminated lots was of less importance compared with the seriousness of yellow fever in unvaccinated soldiers

The disease resembled most closely the so called catarrhal or epidemic infectious jaundice from which it was indistinguishable Usually the onset was gradual until the appearance of jaundice The prodromal symptoms were increased fatiguability lassitude and anorexia Among the gastro intestinal symptoms nausea vomiting and diarrhea were noted Pain in the right upper quadrant of the abdomen lower chest wall neck and shoulders was an important symptom for a number of patients Fever was either absent or slight Pains in the joints and urticaria were present in about 20 per cent of the cases The liver was frequently enlarged and tender Ascites was encountered in some patients Hemorrhagic phenomena were noted in more severe cases as well as albuminuria Dark-colored urine light colored stools and icterus were usually noted The icteric indices ranged from 15 to 200 Liver function tests indi cated various degrees of disturbance of hepatic function Hypopro thrombinemia also was reported The leucocyte count was usually normal at times with a relative lymphocytosis

In most instances the disease was mild In a smaller number it was more severe with various stages of hepatic insufficiency In general recovery followed in four to eight weeks and in the fatal cases death usually occurred in two to six weeks

The chief pathologic lesions in autopsy material were those of acute or subacute yellow or red atrophy of the liver Unlike many types of destructive hepatic disease this form did not have fatty changes as a conspicuous feature Destruction of liver tissue and re

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moval of debris in this condition were invariably accompanied by an inflammatory reaction, justifying the term of hepatitis' The extensive damage observed in the rare fatal cases was not duplicated in those who survived In soldiers who died from accident or disease subsequent to an attack of jaundice, little or no evidence of preceding hepatic damage was found Two sorts of pathologic processes in the liver were described injury of cord cells, varying in degree from the slightest detectable to massive necrosis and lysis, and cellular accumulation about the portal triads It is suspected by some that the latter phenomenon might be responsible for obstructive features of the disease and perhaps even for obstruction to portal blood flow in cases that developed ascites It has also been suggested that changes involving the liver parenchyma constituted the earlier pathologic process responsible for some of the prodromal symptoms and the enlarged tender liver

Weil s Disease

(Spirochetal Jaundice, Leptospiral Jaundice, Leptospirosis or Spirochaetosis icterohaemorrhagica, Typhus bilieux, Epidemic Jaundice)

Weil s disease is a specific febrile infection caused by a spirochete (Leptospira icterohaemorrhagiae) Many of the synonyms listed above are confusing, as they are likely to give the wrong impression concerning the disease Spirochetal and leptospiral jaundice are not adequate terms, even though they convey the etiological meaning of the disease process, since jaundice is present in approximately only two thirds of the cases Moreover, they are general terms and include also other types of leptospiral infections For example L hebdomadis and L autumnalis cause the so called seven day fever and Hasmi respectively in Japan Leptospira canicola carried by and causing disease in dogs, is transmissible to man The term epidemic jaundice should be limited to acute catarrhal or infectious jaundice caused by a virus, it is really more epidemic in nature than Weil s disease.

This disease is not diagnosed as frequently as it should be, and is probably more prevalent in the United States and abroad than is apparent from reports in the literature In San Francisco it has been ascertained that when the disease is carefully searched for, it

is not difficult to find Medical textbooks fail to describe it adequately emphasis is often placed on chills and splenomegaly which are rarely present Many practicing physicians consider the condition too rare to include it in the differential diagnosis and the fact that about a third of the cases never develops jaundice is also not generally appreciated Even when this possibility is thought of the physician frequently finds himself handicapped by the absence of proper laboratory facilities Laboratory personnel in an average hospital are not familiar with the precautions to be observed in establishing the diagnosis in each of the four distinct stages of the disease

Leptospira icterohaemorrhagiae is transmitted to man from infected rats The organism has also been found in field mice dogs cats pigs foxes bats poultry horses and other animals The vast majority of human cases probably come from direct contact with the excreta of rats It is possible that a rat bite may occasionally transmit the disease Human infection ordinarily results from the ingestion of food or water contaminated with the urine of infected rats A considerable number of human infections have occurred through the skin of bathers, sewer workers and barefooted workers in rice fields In these instances the virus probably enters the body through cracks cuts and scratches on the feet hands and elsewhere Man to man infection must be rare or nonexistent Because of the mode of transmission of the disease, those engaged in the following occupations render themselves particularly vulnerable sewer workers miners butchers fishermen and fish handlers workers in breweries and slaughterhouses rice field workers and men in the armed forces remaining for days in wet foxholes Most cases occur in males The sex incidence is no doubt conditioned by the occupational hazard

There are no definite seasonal variations Although sporadic cases may occur throughout the year there appears to be a somewhat increased incidence in the late spring and early fall probably because of increased rainfall and the consequent establishment of more favorable environment for the leptospira For the same reason an increased incidence may be expected during the winter months on the West Coast of the United States

During the initial or septicemic stage of the disease the leptospira invade many organs among them liver kidneys and muscles However the causative organism can be demonstrated in his

tological sections of the kidney and heart only, as the early immunological response leads to destruction of leptospiras in other organs

In the liver, the changes vary between the two extremes In mild cases there may be noted merely biliary stasis and infiltration of portal spaces with leucocytes, whereas in severe infections parenchymal necrosis is present ordinarily only focal in distribution but at times diffuse enough to simulate the condition of acute liver atrophy but without decrease in liver size Particularly in cases without jaundice the hepatic lesions are relatively insignificant, the chief pathological lesion being localized in the kidneys However, there is always a hepatitis, no matter how mild the infection The kidney is usually enlarged The tubular portion is most affected with necrosis of the epithelial cells and many casts The glomeruli may be swollen and filled with exudate and bile precipitate Extensive hemorrhages may simulate hemorrhagic nephritis It is not clear whether the renal damage, chiefly tubular, is toxic in origin and due to spirochetes or is rather attributable to bile (biliary nephrosis) Marked urinary changes are associated with the renal lesions

The skeletal muscles may show only microscopic lesions such as degeneration of muscle fibers cellular infiltration, and hemorrhage These changes are considered by some to be in certain aspects quite characteristic of the disease, to the extent that they may materially help in establishing the diagnosis For biopsy the specimen is best removed from the calf muscle, where the involvement is known to be most severe

As a result of the local action of the organisms on the vessel wall, and/or prothrombin deficiency diffuse capillary hemorrhages occur in the skin serous coverings and visceral organs Hemorrhages may attain such proportions as to give rise to hematemesis, melena, hemoptysis, hematuria, epistaxis, or purpura

At least microscopic lesions appear in many other organs but it is evident that the most severe pathologic lesions are in the kidneys in all cases and also in the liver in some When the liver is markedly affected the combination of renal and hepatic involvement may be termed the hepatorenal syndrome This syndrome, not infrequently observed in many instances of liver disease of diverse etiol

ogy, may be said to assume its most characteristic and full blown picture in Weil's disease

How can jaundice be explained in those patients in whom the autopsy reveals only minimal lesion in the liver? To circumvent this difficulty increased hemolysis has been proposed as the chief mechanism responsible for icterus Erythrophagocytosis so frequently noted in the spleen presents evidence in favor of this view Most likely, both the liver changes (toxic edema and the parenchymal necrosis) and increased hemolysis are operative preponder

TABLE XIX

WEIL'S DISEASE
Clinical Features—Weil's disease is a specific febrile infection caused by L. icterohaemorrhagiae and is transmitted to man through the ingestion of food or water contaminated with the urine of infected rats It is thus dependent upon occupational exposure (sewer workers miners butchers workers in slaughterhouses etc) The clinical course is divided into three stages the febrile or septicemic the icteric and the convalescent The first stage lasts from the onset of the disease until the development of icterus lasts only a few days and is marked by an abrupt onset characterized by severe headache chills fever nausea vomiting and myalgia The icteric stage lasts about a week and is accompanied by hemorrhagic tendency apathy and prostration along with indications of meningeal irritation in some cases. The liver becomes enlarged. A uremic like state may supervene with albuminuria oliguria and nitrogenous retention in the blood The convalescent stage begins about the end of the second week
Laboratory Findings—Bile salts and bilirubin are present in the urine The van den Bergh reaction is direct positive In the initial stages Leptospira can be demonstrated in the blood During the second week of the disease the organisms disappear from the blood and appear in the urine From the third week on the blood of the patient contains specific agglutinins against the infecting organism these can be demonstrated by agglutination tests
Differential Diagnosis—The icteric period if present may be confused with catarrhal or infectious jaundice The distinguishing feature is hepatic enlargement in the absence of splenomegaly and lymphadenopathy However a definite diagnosis depends upon the proper use of specific laboratory procedures mentioned above The physician will be able to make the correct diagnosis only by keeping in mind the possibility of the presence of this disease

antly in producing jaundice Some workers have demonstrated marked inflammation of the smallest biliary ducts and concluded that jaundice was due to obstruction in these passages

The clinical course of the disease is more or less arbitrarily divided into four stages There is no absolute line of demarcation but such division into stages is very convenient for descriptive pur poses Generally speaking the disease is characterized by abrupt onset high fever chills myalgia arthralgia vomiting extreme pros tration jaundice hepatomegaly hemorrhagic tendency conjuncti val injection disturbance of heart function and varying degrees of renal failure with albuminuria and azotemia The condition is essentially a hepato renal syndrome

The febrile or septicemic stage lasts from a few days to a week The onset is frequently sudden with chills followed by fever nausea vomiting myalgia headaches anorexia diarrhea or consti pation and prostration Abdominal pains or discomfort arthralgia and tenderness in the back and calves are common Unlike most acute infectious processes the severe muscular aching associated with tenderness of the muscles has in Weil s disease a pathologic basis that is one of the primary distinguishing features of the dis ease An upper respiratory infection with cough and bloody expec torations may simulate pneumonia The fever is usually high rang ing between 101 and 104° F Conjunctival injection may be a con spicuous feature in many patients and is believed by some to be quite characteristic if not diagnostic of the disease However it is seen also in some cases of epidemic jaundice This stage is char acterized by spirochetemia lack of circulating antibodies and ab sence of spirochetes in the urine Leptospiras may be demonstrated in the circulating blood by means of microscopic dark field exami nation

The hepatic or icteric stage lasts about a week In contrast to the initial stage it is characterized by the absence of spirochetemia development of circulating antibodies and the excretion of nu merous spirochetes in the urine Jaundice gradually makes its ap pearance in about two thirds of all cases The liver becomes en larged tender and painful and the spleen palpable only occasion ally The fever continues and the patient is usually toxic apathetic and prostrated although the initial gastro-intestinal symptoms with myalgia arthralgia and headache tend to disappear There is evi

dence of hemorrhagic diathesis with petechial and echymotic spots in the skin and mucous membranes epistaxis melena hematemesis hemoptysis and gingival bleeding Cardiovascular symptoms and signs attain prominence such as hypotension and occasionally car diac dilatation and hemic murmurs Gallop rhythm bradycardia cardiac arrhythmias pericardial friction rub and electrocardio graphic evidence of disturbances of conduction have all been de scribed It is a reversible type of heart disease (acute myocarditis) and in most cases the heart returns to normal during convalescence Central nervous system complaints include headache restlessness delirium and toxic psychosis In very severe cases there are indi cations of meningeal irritation i e stiff neck with retraction of the head and other signs The distinguishing feature in the icteric period which may be confused with infectious jaundice is hepatic enlargement in the absence of splenomegaly and lymphadenopathy Most fatalities occur in this stage of the disease

The nephritic or uremic stage may be coexistent with the one above described and the two frequently merge without any line of demarcation Oliguria and albuminuria which might have been present soon after the onset of the disease now become accentu ated and oliguria progresses to anuria in fatal cases Red and white blood cells are found in the urine along with occasional casts and there is nitrogenous retention in the blood as the kidney function declines to mark the uremic stage The convalescent stage begins about the end of the second or beginning of the third week of the disease though occasionally it may be delayed till the fifth week Jaundice subsides but sometimes may last a few weeks With the disappearance of icterus clinical evidence of an anemic state may become apparent More urine is secreted the temperature returns to normal and hemorrhages cease However the patient may still feel prostrated In some instances there may be recurrence of fever but in the absence of other symptoms The more atypical forms of the disease as taken from the various sources in the literature are as follows (Bertucci)

1 The nonicteric type generally with a mild course the most fre quently encountered variant
2 Malaria like onset fever lasting for 24 to 48 hours only late al buminuria hemorrhages during afebrile period

3 Complete absence of pains slight fever with prostration albuminuria and jaundice
4 The pneumonic or influenzal type with massive consolidation of one or both lungs
5 The melena type with fever and profuse hemorrhage
6 The cerebral or meningeal type with early unconsciousness and delirium
7 The cardiac or nephritic type simulating acute congestive heart failure
8 Intensely jaundiced type with black vomitus
9 The yellow fever type with black vomitus
10 Chronic meningeal and a chronic icteric form

Albuminuria red and white blood cells and casts in the urine and nitrogenous retention in the blood during the second or third stage of the disease have already been mentioned Kidney function tests show an impairment about a week after the onset and bilirubin with excess urobilinogen are present in the urine The icterus index may reach a value as high as 200 units or even higher The van den Bergh reaction is usually of the direct type There is commonly a hypochromic microcytic anemia present The leucocyte count may be normal or increased The spinal fluid is often under increased pressure and the Pandy reaction weakly positive The cell count on the spinal fluid may range from normal to 2000 or 3000 more frequently not above 300 the neutrophils and lymphocytes being present in about equal proportions The sugar and chlorides are normal

The diagnostic laboratory procedures vary with the stage of the disease as in the case of typhoid fever A definite diagnosis can be established only by the laboratory tests that consist of (1) demonstration of the leptospira in the blood by direct dark field examination culture of the blood or inoculation of the blood into a suitable laboratory animal (2) detection of the organism in the urine and inoculation of laboratory animals with it (3) serological examination (4) Fontana and Levaditi stains of tissues and (5) muscle biopsy Unfortunately there are fallacies inherent in each one of these tests

During the septicemic stage a dark field examination of the patient s blood is the best method of diagnosis The recognition of the organism by this procedure is by no means an easy one in the

presence of myriads of minute particles of fibrin and other partiall precipitated proteins normally seen in blood and agitated in con stant Brownian movement Artefact spirochete like bodies simila to those reported by Schultz can be mistaken for leptospira and thu serve as a possible source of error in the dark field examinations These pitfalls make the animal inoculation or culture a desirabl confirmatory procedure After injection of patient s blood or urin into the guinea pig typical lesions are observed in the laborator animal with the recovery of the causative organism from them Oc casionally leptospira have been recovered from the cerebro spina fluid

After the first week of the disease the urine should be examinec for these organisms Because there frequently are spirochetes of many varieties in normal urine direct dark field examination of the speci men is not satisfactory even when it is centrifuged Unfortunately guinea pig inoculation with the sediment is often unsatisfactory In the third and subsequent weeks of the disease the organism produces in the host very specific agglutinins which can be meas ured These are among the most specific antibody reactions known The demonstration of specific antibodies in the patient s serum i carried out either by means of the Pfeiffer reaction or the direct agglutination of the same strain

Muscle biopsy is not very practical but may be diagnostic in doubtful cases The changes seen on microscopic examination of the gastrocnemius muscle are vacuolation swelling loss of striation, and hyalinization of muscle fibers along with infiltration with neutrophile and plasma cells

Levaditi Fontana and Giemsa stains are used on tissues obtained at autopsy of the fatal cases or of the organs of experimental ani mals after inoculation with blood or urine of patients

Yellow Fever

The physician in the United States need not be concerned with this disease The following description is included for the benefit of the reader who may find himself in those parts of the world where yellow fever is still encountered As the author has not had any personal experience with this disease the data below have been freely drawn upon from the literature The bulk of the informa

tion is founded upon the reports of Klotz and Simpson, Klotz and Belt, Soper, and the authoritative article by Sawyer.

Yellow fever still remains a virus disease of unknown identity. Autopsy reveals a pale yellow, fatty liver, a pale, flabby heart, tense swollen kidneys, and hemorrhages into the gastro intestinal tract, pericardium, pleura lung, meninges, and bladder. The most important microscopic lesions consist of degenerative changes such as fatty degeneration and necrosis of the parenchyma with almost no inflammatory reaction Many organs and tissues are affected by these changes, but those of the liver, kidneys, spleen, and heart are most important

In spite of the normal *size* and relatively normal gross appearance of the liver, the extent of hepatic injury revealed by microscopic examination is amazing The necrosis involves a variable amount of liver tissue, at times most of the parenchymal *cells* In extreme injury only a few cells recognizable as hepatic parenchyma remain Fatty changes are always found and the stroma remains undamaged Thus the liver lesion in yellow fever is distinctly not a hepatitis, but rather a noninflammatory parenchymal necrosis The reaction in the kidneys is also degenerative, not inflammatory, while the renal lesion varies from cloudy swelling to fatty degeneration and necrosis In the spleen, which remains unaltered in size, microscopic changes are often marked Degenerative, noninflammatory changes may be found in all parts of the myocardium The *lesions are not equally severe in all organs of the same patient* When the liver *is* badly damaged the heart may escape lightly, or vice versa, whereas in other cases the kidneys seem to bear the brunt of the attack However, in all fatal cases an appreciable necrosis of the liver takes place This is the most constant, as well as the most characteristic, lesion of yellow fever

The incubation period averages probably about five days In the classic case, *following* a typical onset with symptoms of severe infection there occur during the second stage albuminuria, hemorrhages, and jaundice. The classic attack may be mild if the hemorrhage *does not become* excessive and the kidneys continue to function Severe oliguria and anuria are found only in cases presenting hemorrhagic diathesis and jaundice

The onset is rapid and dramatic. Within a period of a few hours an apparently well person is transformed into a very sick patient.

The pulse and temperature reach their fastigia on the first [illegible] after that there is a tendency for both to decline the pulse [illegible] sooner and more rapidly than the temperature Thus [illegible] pulse and the temperature is considered as the most constant [illegible] characteristic individual finding in yellow fever The temperature often shows a secondary rise but the bradycardia continues [illegible] from the third day on except when a lethal outcome is [illegible] ing Severe prostration headache backache pain in the legs, malaise nausea and vomiting stand out in sharp contrast to the paucity of physical findings at the onset The temperature reaches normal or subnormal levels at the end of the first 48 to 72 hours, and the patient begins to look better for a short period, but after the end of the third day there is intensification of previous symptoms such as nausea and vomiting and there appears evidence of overwhelming intoxication This second stage of the disease is marked by the triad of albuminuria hemorrhagic diathesis and jaundice Icterus varies from very slight to marked Hemorrhages may be so severe as practically to exsanguinate the patient and are often the immediate cause of death The onset of albuminuria is rapid and heavier than would be expected in severe [illegible] nesses due to other causes Anuria apparently depends on an entirely different mechanism from that producing [illegible] teinuria The former seems to be related to the destructive [illegible] in the liver and follows hepatic involvement whereas [illegible] may precede and even be independent of other signs of [illegible] intoxication

In [illegible] [illegible]entally produced yellow fever (rhesus [illegible] is ev[illegible] [illegible] tion as shown by the [illegible] lem

The clinica[illegible] [illegible] seen as an inapparent infect[illegible] [illegible] acquired immunity as an abortive infection [illegible] or as an incomplete attack exhibiting the usual trend [illegible] with the exception of jaundice hemorrhage and anuria

While Weil's disease and yellow fever bear some [illegible] blance and are both characterized by hepatitis the [illegible] causes specific histologic changes in the liver that can [illegible] tiated from those found in leptospirosis icterohaem[illegible] [illegible] In

TABLE XX

DIFFERENTIAL DIAGNOSIS OF PARENCHYMATOUS JAUNDICE (ACUTE FORMS)

	Acute Catarrhal or Infectious Jaundice	*Weil's Disease*	*Yellow Fever*	*Acute Liver Atrophy*	*Relapsing Fever*	*Septicemia with Icterus*
Geographic distribution	universal	universal	Amazon Basin, West Africa	universal	in many parts of the world	universal
Causative agent	virus of unknown identity	spirochaeta icterohaemorrhagiae	virus of unknown identity	virus, bacteria, chemical and vegetable poisons	spirochete of Obermeier	various bacteria
Incubation period	to 4 weeks	4 or 5 days to 2 weeks	about 5 days	variable	2 to [illegible] days average 5 7 days	variable
Mode of onset	most often with gastric and enteric disease	sudden, with chill and high fever	very rapid and dramatic onset with period of a few hours with symptoms of severe infection	frequently the same as in catarrhal or infectious jaundice	abrupt with a chill followed by high fever	variable
Predominant subjective symptoms	lassitude anorexia flatulence headache nausea occasional vomiting frequently no prominent or severe complaints	intense muscular pains and headache prostration vomiting	similar to symptoms of Weil's disease	at onset as in catarrhal jaundice with intensification of symptoms as [illegible] in the disease	intense headaches, joint pains, nausea, vomiting, photophobia	headache prostration, and [illegible]
Muscular pain	not conspicuous	most conspicuous	may be present	common	not uncommon	rare
Chills and fever	absent or not marked	marked and prominent features	temperature reaches high peak rapidly on 1st day. Remission at end of 2 or 3 days lasting 3 to 48 hrs followed by relapse	no conspicuous fever more marked later in the disease	may be prominent relapsing fever	chills sepsis-like fever sweats
Hemorrhagic diathesis	rare	common	common	occasionally	epistaxis	not conspicuous
Outward appearance	patient often does not appear very ill	acutely ill	acutely ill	acutely ill later in the disease	acutely ill	acutely ill
Conjunctival injection	seen occasionally	characteristic	often present facial congestion	none ordinarily	none ordinarily	none ordinarily
Meningeal signs	rare	frequently present	absent	may be present	frequently present	may be present
Jaundice	variable in intensity	when present is usually marked appears 5 to 9 days after onset	intensity increases appears in 3rd day of disease	usually marked	slight to moderate often appearing early on 2nd or 3rd day of disease	slight to moderate
Liver	enlarged and tender	enlarged and tender	normal size or slightly enlarged	characteristically diminished in size	enlarged	normal in size
Spleen	frequently enlarged	seldom enlarged	not enlarged	variable	frequently enlarged	may be enlarged

yellow fever the liver shows hyaline areas of Councilman necrosis extensive fatty degeneration and cellular dissociation of such an extreme degree that all lobular structure is lost Councilman necrosis is never seen in Weil s disease nor is there as much fatty infiltration or such extensive separation of the liver cells

Toxic Hepatitis of Systemic Disease

Some workers designate as toxic hepatitis the liver involvement secondary to some underlying systemic disease Another group of toxic hepatitides consists of cases of chemical and vegetable (mushroom) poisoning We shall first consider cases of jaundice and hepatitis arising in the course of a systemic infection

In infections where hepatic involvement is the dominant feature (catarrhal or infectious jaundice Weil s disease and yellow fever) the liver injury has the character of a second disease in that the stage of infectivity usually ends as jaundice appears In all of these conditions permanent specific immunity occurs By contrast in the group here considered are included infections in which jaundice is only a complication and may occur in various stages of the major infection

General Infections Associated Occasionally with Jaundice

Actinomycosis	Periarteritis nodosa
Gonococcal Infection	Relapsing Fever
Infectious Mononucleosis	Septicemia
Lobar Pneumonia	Syphilis
Malaria	Tuberculosis
Oroya Fever	

Syphilis

Early Syphilis Jaundice occurring in syphilis was noted as early as 1585 by Paracelsus It was early appreciated that hepatic involvement in acute syphilis might take one of two forms—relatively benign syphilitic hepatitis or grave icterus a fulminating acute yellow atrophy The latter as a complication of acute untreated syphilis is rare and is observed more frequently following arsenical therapy The incidence of jaundice in all patients with early syphilis has been estimated as 0 3 to 3 per cent

The actual pathogenesis of jaundice has been difficult to establish because of the paucity of pathological material Only one observer (Warthin) has reported the demonstration of T pallidum in the liver of a patient in the secondary stage of adult syphilis Many theories of the mechanism of icterus have been advanced by different workers The introduction of arsenical therapy has

TABLE XXI

SYPHILIS OF THE LIVER
Clinical Features—The occurrence of jaundice during the secondary stage of syphilis is rare Icterus usually makes its appearance simultaneously with the cutaneous roseola and may be the only symptom while in some patients it is accompanied by fever gastro-intestinal disturbances and malaise Clinically acute syphilitic hepatitis differs little from catarrhal jaundice The illness lasts from two to five weeks
Laboratory Findings—These are similar to the laboratory findings of catarrhal jaundice In addition there is a positive blood Wassermann reaction
Differential Diagnosis—Only the demonstration of the spirochetes or the positive serological reaction with or without a chancre or secondary eruption gives presumptive evidence that syphilis is the cause of jaundice Prompt response to antiluetic therapy serves as confirmatory evidence In the case of a patient treated for syphilis prior to the onset of jaundice differentiation from arsenical hepatitis may be extremely difficult.

further complicated the question of syphilitic jaundice The hepatotoxic action of the organic arsenicals has been well demonstrated both clinically and experimentally The incidence of jaundice in early syphilis has been observed to increase from 0 18 per cent in untreated patients to 1 37 per cent in those under treatment with arsenicals While some of these cases of icterus developing during treatment are clearly manifestations of arsenic toxicity, others represent luetic hepatitis occurring because of insufficient treatment and may thus respond to further antiluetic therapy Still others may be instances of intercurrent acute catarrhal or infectious jaundice In the armed forces a rather striking parallelism was noted between the incidence of postarsphenamine jaundice in syphilitic and that of infectious jaundice in nonsyphilitic men in the same locations

The mechanisms responsible for the occurrence of jaundice in early syphilis have been variously postulated Compiled from the literature they are as follows (Leonard)

Untreated (due to syphilis)
Roseola of bile ducts
Lymphadenitis compressing bile ducts
Spirochetosis
Hyperemia of intrahepatic bile ducts
Duodenal catarrh
Hemolytic jaundice
Syphilitic hepatitis

Treated
Herxheimer reaction
Syphilitic hepatitis with inadequate treatment hepatorecurrence
Arsenical hepatitis
Bismuth hepatitis
Mercurial hepatitis

Coincidental
Catarrhal jaundice
Cholelithiasis

Obviously it may be very difficult to decide in any one particular case the precise etiology of jaundice especially when the patient is under antiluetic therapy Perhaps the following criteria can be depended upon for a satisfactory establishment of syphilitic etiology of icterus (1) the patient must have definite clinical and/or serological evidence of active luetic infection (2) the condition must exist in the absence of other common causes of jaundice (3) the specific antiluetic treatment must lead to the cure of jaundice

Clinically acute syphilitic hepatitis differs little from catarrhal jaundice its chief manifestations are icterus and enlargement of the liver There is usually malaise and may be some fever and gastrointestinal symptoms The patient complains of nausea and vomiting and sometimes diarrhea The stools are acholic at first and the urine dark colored The blood bilirubin is increased and the liver function tests reveal hepatic functional impairment The illness lasts from two to five weeks Only the demonstration of the spirochetes or the positive serological reaction with or without a chancre or secondary eruption gives presumptive evidence that

syphilis is the cause of jaundice Prompt response to antiluetic therapy may be considered as confirmatory evidence

Acute yellow or red atrophy associated with syphilis is also clinically indistinguishable from that of other causes it usually begins insidiously like a benign hepatitis often with hepatomegaly There may or may not be fever malaise muscular pains nausea or vomiting Pruritus occasionally is complained of Then rather suddenly there comes a turn for the worse in which the liver rapidly becomes smaller and crystals of tyrosine and leucine appear in the urine This condition is rare for there have been reported in the literature only about 60 cases of acute liver atrophy in early syphilis proved at autopsy to be unrelated to arsenical treatment Since the introduction of the arsenicals there has been a considerable increase in the incidence of acute liver atrophy in the syphilitic population

Late Syphilis Gummatous hepatitis is only rarely associated with jaundice When it is icterus probably depends upon a lesion involving the main bile ducts ascites may develop on the same mechanical basis When this occurs the differential diagnosis between portal cirrhosis and gummatous hepatitis becomes extremely difficult

Congenital Syphilis Jaundice has been reported to occur occasionally with congenital syphilis

Pneumonia

The cause of icterus in pneumonia is not fully understood Hemolytic action of the pneumococcus and parenchymal liver damage have been implicated by different observers Focal areas of parenchymal liver necrosis have been noted However frequently the liver does not show sufficient damage on the post mortem table to attribute jaundice to hepatic injury

Icterus appears to be more frequent with pneumonia involving the right lower lobe It may be difficult to differentiate this septic jaundice from obstructive and other types of icterus The restricted mobility of the chest rapid respirations dilatation of the alae nasi the physical findings in the chest and marked polymorphonuclear leucocytosis with the shift to the left help the clinician to realize that he is dealing not with jaundice of primary liver or biliary tract disease but rather with a septic condition

Septicemias

In acute septicemias, jaundice of varying degree is an occasional symptom and generally of unfavorable prognosis The organisms commonly concerned are the pneumococcus, hemolytic streptococcus, staphylococcus, and the Welch bacillus Some cases of severe jaundice in the newborn belong in this group Hemolytic and bacterial toxic agents suggest a combination of factors responsible for jaundice Occasionally, extensive liver necrosis is also found However, these isolated lesions, even when extensive, are often noted without jaundice Cholangitis, liver injury, and extensive blood destruction are probably all operative in the production of clinical icterus Puerperal infection caused by Clostridium welchii is frequently associated with deep jaundice. Icterus may occasionally develop in meningococcemia

The mechanism of jaundice production varies with different organisms The Welch bacillus infection is the best understood It is a fulminant hemolytic anemia with hemoglobinuria, methemoglobinemia, and hematinemia The same type of jaundice may occur in the rare septicemia caused by the anaerobic staphylococcus The mechanism of jaundice from hemolytic streptococcus septicemia is not well understood. Only diffuse cloudy swelling of the liver cells has been found on necropsy and the degree of degeneration bears no correlation with the degree of icterus A small distinctive group has been described in which focal necrosis is found throughout the liver, and streptococci are easily demonstrable in these areas There are no abscesses and the lobules do not show central necrosis. Recently it has been claimed that jaundice may be a complication of bacillary dysentery It is probable that there were two different epidemics, one of dysentery and the other of infectious jaundice

The picture of sepsis, with chills, sweats, septic temperature, and a positive blood culture, helps to establish the identity of icterus as secondary to an underlying systemic infection

Tuberculosis

In contrast to syphilis, tuberculosis comparatively rarely produces jaundice, even in instances of miliary tuberculosis of the liver. Icterus is usually mild Except in rare cases of obstructive jaundice due to tuberculous bile-duct involvement, the icterus appears to be attributable to liver-cell damage.

Actinomycosis

Jaundice is rare in actinomycosis of the liver which usually is secondary to a process in the intestinal tract at the ileocecal region

Periarteritis Nodosa

Most common as single causes of hepatic infarction are periarteritis nodosa of the branches of the hepatic artery and embolism in subacute bacterial endocarditis In true anemic infarction of the liver there is complete necrosis of all the tissue elements The outstanding clinical symptoms are pains across the upper abdomen or pains limited to the hepatic region with marked tenderness and spasticity over the right upper quadrant Vomiting occurs and jaundice may develop Fever and leucocytosis are commonly observed

Lymphogranuloma Venereum

Jaundice due to hepatic localization of the virus of lymphogranuloma venereum has been reported

Malaria

Malarial paroxysm may be associated with acute liver damage producing focal parenchymal necrosis This may be toxic or anoxemic in origin Toxemia anoxemia (from anemia) and excessive hemolysis probably operate conjointly to cause impairment of liver function and hepatic damage Jaundice is rarely frank and is usually subclinical with direct van den Bergh reaction

Gonococcal Infection

Recently it has been brought to general attention that jaundice is comparatively frequent in the course of a gonorrheal infection The condition resembles that of catarrhal jaundice Prolonged cases of gonorrhea are particularly prone to develop this condition Other complications of gonorrheal infection such as endocarditis may develop in addition to jaundice in the same patient

Relapsing Fever

Well marked jaundice appearing quite early often on the second and third day of the disease is not uncommon The other signs and symptoms are fever hemorrhages muscle pains and occasionally signs of meningitis Both liver and spleen may be enlarged The pathology is analogous to that in secondary syphilis Leucocytosis

is present The disease resembles leptospirosis The first febrile period in relapsing fever and the first stage of Weil s disease both last about six days relapses occur in both diseases during the third week Leucocytosis is also present in both conditions However, splenomegaly is rare in Weil s disease The diagnosis of relapsing fever is based on finding large spirochetes of Obermeier in stained films of blood taken during relapses

Infectious Mononucleosis

Acute infectious mononucleosis is occasionally complicated by icterus The clinical course is similar to that of catarrhal jaundice, although somewhat milder There are no pathological reports on the liver available but as the clinical features suggest ordinary infectious jaundice it seems valid to assume that icterus is caused by hepatitis It was thought by some observers to be due to occlusion of the common bile duct by swollen lymph nodes However it is now generally accepted that the presence of simple inflammatory lymph nodes in the porta hepatis is not adequate to cause obstruction The prodromal symptoms of upper respiratory infection followed later by lymphadenitis palpable spleen and relative lymphocytosis are common to both infectious mononucleosis and catarrhal jaundice Only a careful examination of the blood smear for typical lymphocytes of glandular fever (atypical nucleus fenestration of the nucleus) and the positive agglutination for heterophile antigen (Paul Bonnell test) enable one to distinguish between the two *

TOXIC HEPATITIS DUE TO CHEMICAL POISONS

Sporadic cases of jaundice that might well be due to toxic agents are probably more common than is apparent for the cause is often undiscovered There are three major types of action of chemical poisons in regard to their deleterious effect on the liver Some chemicals may induce direct injury to the liver parenchyma, they readily produce liver necrosis in experimental animals (phosphorus chloroform carbon tetrachloride) Others primarily induce a hemolytic process with secondary injury to the liver cells by the products of

* However abnormal lymphocytes appear in epidemic hepatitis. Liver function tests frequently demonstrate hepatic impairment in cases of infectious mononucleosis with and without jaundice Apparently the liver is not uncommonly involved in this disease which like infectious hepatitis may also be caused by a virus

hemolysis some of the chemicals in this group may in addition be directly injurious to the liver cells (phenylhydrazine) Finally idiosyncrasy hyper susceptibility and allergic sensitivity are the determinant factors with other chemicals (drugs such as arsphenamines sulfonamides and cinchophens) By idiosyncrasy is meant an unusual effect of a drug for which no explanation can be found

Whereas in the various types of infectious jaundice the recovery is followed by the development of a specific immunity in the case of chemical jaundice there is a greater sensitivity to many hepatotoxic agents after recovery

The list of liver poisons below presented is adopted after Ottenberg and Spiegel and Greene

Jaundice due to chemicals

A *Direct injury to liver parenchyma*
 1 *Therapeutic agents* gold *chloroform* arsenic *carbon tetrachloride* ether iodoform avertin etc.
 2 *Accidental contacts* amanitotoxin nitrobenzene *phosphorus* burns etc
 3 *Industrial hazards* tetrachlorethane carbon disulfide trinitrotoluene etc
 4 *Experimental agents* *selenium* copper etc

B *Primary hemolysis with secondary injury to the liver cells*
 1 *Therapeutic agents* phenylhydrazine *sulfonamide compounds* incompatible blood in *transfusions*
 2 *Accidental contacts* snake *poison* bean poison
 3 *Industrial hazard* arsine
 4 *Experimental agents* distilled water toluendiamine

C Idiosyncrasy *hyper susceptibility and allergic sensitivity*
 1 *Therapeutic agents* arsphenamine *cinchophen* liver extracts bismuth *sulfonamides mercury*

Only the most commonly encountered types of chemical poisoning will be discussed here These are cases of jaundice due to arsenicals sulfonamides gold cinchophen *carbon tetrachloride* and phenylhydrazine Mushroom poisoning will also be mentioned

Arsenic

Post Arsphenamine Jaundice Jaundice following administration of arsphenamine is usually ascribed to injury of the liver parenchyma The autopsy findings in some cases confirm the hepatogenous character of jaundice by histologic studies showing marked

degenerative changes in the hepatic lobule In patients with non fatal icterus similar though less advanced parenchymal damage is *generally assumed to be present this has been demonstrated in a* few instances In such cases arsphenamine icterus simulates catarrhal jaundice quite closely In fact it has been stated that arsphenamine merely lowers the resistance of the liver to the virus of epidemic hepatitis This assumption however conflicts with the observation that should paratherapeutic icterus be regarded as catarrhal jaundice the proportion of syphilitic persons in the latter group would be astounding approximately 20 per cent Also there is another observation that over a five year period paratherapeutic jaundice among syphilitic persons was four times more frequent than catarrhal jaundice and acute yellow atrophy

In rare instances acute liver atrophy results from arsphenamine therapy Still another pathological process of arsphenamine jaundice is one principally constituted by pericholangitis inside the liver with formation of bile thrombi in the finer biliary radicles causing an intrahepatic obstruction to the outflow of bile (See Fig 10 p 52) The liver parenchyma is seen on liver biopsies to be preserved and essentially intact The selective injury of the finer biliary radicles within the substance of the liver may be produced by a number of toxic agents as for example in experimental toluendiamine poisoning The pathological process is similar to that described by Eppinger as the cholangiolitic type of catarrhal jaundice in distinction to the ordinary hepatocellular variety In all these instances the inflammatory changes about the biliary canaliculi with formation of bile thrombi within their lumen are the cause of intrahepatic obstructive jaundice This sort of injury with an obstructive type of reaction may be very difficult to distinguish from obstructive jaundice of extrahepatic variety

In the case of any individual patient who during the course of antiluetic therapy develops jaundice the questions to be decided are (1) Is it a case of arsenical icterus? (2) Is it a hepato recurrence i e syphilitic hepatitis with inadequate treatment? Or (3) is it an intercurrent infection i e catarrhal jaundice in a case where the liver resistance to the virus of infectious hepatitis has been lowered by the heavy metal?

Lichtman lists the essential clinical differences between arsphenamine and catarrhal jaundice as follows (1) An asymptomatic onset

and course are more common in the *postarsphenamine* group (2) Pain and tenderness in the abdomen is a bit more common in the infectious group as are headache, malaise, and weakness (3) Constipation is more common and diarrhea uncommon, in the infectious group (4) Indigestion and loss of appetite are more common

TABLE XXII

ARSENICAL HEPATITIS
Clinical Features—Following treatment with arsenicals the jaundice may set in early or late The early type follows within one to two weeks after the institution of therapy The late variety is delayed for several months Icterus may be the only symptom or may be associated with fever, chills, malaise nausea vomiting, and pain in the right upper quadrant of the abdomen Liver and spleen may become enlarged. The stools are clay colored
Laboratory Features—Laboratory data point to intrahepatic biliary obstruction The van den Bergh reaction is direct positive and bile pigments are absent from the stool The obstructive nature of icterus is indicated by hypercholesterolemia elevated blood phosphatase and negative cephalin-cholesterol flocculation test
Differential Diagnosis—Intrahepatic obstruction present in this condition makes the differentiation from the extrahepatic biliary obstruction imperative It may be difficult to differentiate arsenical hepatitis from infectious or catarrhal jaundice as the symptoms of the two may be identical The chief step in making the correct diagnosis is the knowledge that arsenical therapy has been given Differentiation from syphilitic hepatitis is not difficult because of rarity of luetic etiology in jaundice

also in the infectious group Other than the evident icterus, which is of varying degree, the most significant physical finding in both groups is a palpable liver The liver is more commonly tender in infectious jaundice, whereas a palpable spleen is a bit more common in the postarsphenamine group Lichtman admits that 'although differences between the two groups are evident, in any given case it is quite impossible to differentiate between them' Most likely, however jaundice developing in a patient under therapy is due to the heavy metal rather than intercurrent infection (catarrhal jaundice) or syphilis itself (hepato recurrence) Moreover, it is best to err on the safe side and discontinue arsenical therapy on the presumption

that one is dealing with postarsphenamine jaundice A patient's un willingness to volunteer or admit on questioning antileutic therapy beclouds the issue

The stage of the disease or the phase of treatment appears to bear no influence The symptomatology in all early cases seems to de pend upon the nature of the pathological lesion, except for the initial symptom of chill followed by fever which is common to all In one group, the chill is followed by fever with malaise, nausea, and sometimes vomiting Occasionally there is a toxic erythema Icterus appears four to eight days later and is accompanied by fatigue, anorexia, diarrhea and itching Tenderness and pain in the hepatic region and splenomegaly may be present but are not constant The second group in which evidently, the essential patho logical lesion is pericholangitis as described above, presents the pic ture of obstructive jaundice with little or no evidence of liver paren chymal involvement Shaking chill and fever with malaise, head ache, and vertigo later followed by anorexia, nausea, and vomiting, constitute the prodromal symptoms Some patients do not have a chill and the initial gastro-intestinal symptoms are accompanied by conjunctivitis or skin lesions There may be fleeting arthralgia, at times quite severe, and edema of the face and/or extremities Jaun dice does not appear until one or more days after the onset of symp toms With the appearance of icterus acholic stools and pruritis are frequently observed, while marked asthenia and considerable weight loss may develop The laboratory tests confirm the obstructive nature of jaundice hypercholesterolemia elevated blood phosphatase (above 10 Bodansky units per 100 cc) and negative cephalin choles terol flocculation test, which is usually positive in the first group It is evident that this type of intrahepatic obstructive jaundice may simulate gross occlusion of extrahepatic biliary passages by gallstones or neoplasm As a matter of fact, in several cases laparot omies have been performed on this false premise The differential feature of great value is the history of administration of arsphena mine In some instances of postarsphenamine jaundice, the clinical picture and laboratory findings are those of acute liver atrophy

Usually the process subsides within three or four weeks In the obstructive group, however, it may persist along with pruritis but in the absence of other symptoms, for several months

A d œ

dev jaundice perhaps two or thre . . . the last injection The clinical picture is usually indistinguishable from that of infectious or catarrhal jaundice and only a history of antiluetic therapy can give the clue to the correct diagnosis

The illness may be of longer duration and serious sequelae are more frequent than in the case of simple catarrhal jaundice When icterus develops late i e a number of weeks after the last injection of an arsenical it may be associated with severe and lasting hepatic injury

Gold

Gold salts are used empirically in the treatment of rheumatoid arthritis and lupus erythematosus A variety of toxic side actions have been observed such as ulcerative gastroenteritis nephritis purpura and agranulocytosis The incidence of toxic reactions is . . te high occurring in about 25 per cen . . .

. . . ptoms and dosage Cumu . . . plays some role There is usually a latent period and jaundice lasts from three to four weeks

Carbon Tetrachloride

Carbon tetrachloride is widely used in industry and as an anthelmintic Its excellent solvent properties non inflammability and inexpensiveness are the reasons for its great popularity both in industry and in the home This chemical is toxic and occasionally fatal to both men and experimental animals Liver and kidneys are primarily affected In fatal cases the most marked microscopic changes are observed in the . . .

. . . the damage is usually limited to the tubular epithelium with degeneration of the cells lining the convoluted tubules

Jaundice following inhalation or ingestion of carbon tetrachloride is particularly apt to develop in alcoholics Fatal or even serious poisoning does not occur in well regulated industries and most of

the recent cases of fatal poisoning have occurred in isolated or individual use of carbon tetrachloride as contrasted to its use in industry

The prominent clinical symptoms and signs are headache nausea and vomiting with occasional hematemesis followed by icterus and later by oliguria anuria and retention of nitrogen Pulmonary complications such as edema and pneumonia may occur With severe renal involvement edema and hypertension are commonly encountered Clinically the condition may closely resemble infectious hepatitis Correct diagnosis often fails to be established because the physician does not discover that his patient has been exposed to carbon tetrachloride as the average layman is unaware of its danger Oliguria or anuria and the development of hypertension at the time of appearance of icterus aid in distinguishing carbon tetrachloride poisoning from infectious jaundice

Phenylhydrazine

This drug is used for treatment of polycythemia vera The therapeutic effect is mediated through production of excessive hemolysis Hepatosplenomegaly and jaundice with abdominal distress nausea anorexia and weakness are the outstanding features of toxic effect The hemolytic component may be a contributory factor in the production of jaundice of hepatocellular origin

Cinchophen

This drug is used for treatment of rheumatism It may produce liver injury in susceptible individuals As with arsphenamine the appearance of jaundice may be delayed as long as two months after the drug has been discontinued The incidence and severity of icterus bear no relation to the size of the dose Occasionally jaundice has occurred after cinchophen has been taken continuously stopped and a small dose resumed Perhaps cinchophen jaundice is due to sensitization Hepatic necrosis is extensive An outstanding phenomenon that distinguishes the pathological process produced by cinchophen toxicosis from others is the associated relative retardation of regeneration

The initial symptoms may be deep jaundice lassitude weakness and anorexia Pruritis may accompany jaundice The stools are clay colored and the urine dark-colored during the stage of intrahepatic obstruction The liver is enlarged but the spleen cannot be palpated

A difficult problem in diagnosis is presented by those patients who develop a late or delayed arsphenamine jaundice perhaps two or three months after the last injection The clinical picture is usually indistinguishable from that of infectious or catarrhal jaundice and only a history of antiluetic therapy can give the clue to the correct diagnosis

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In summary it may be said that toxic jaundice due to chemical poisoning obviously can be diagnosed only on history of exposure to hepatotoxic agents as the clinical course otherwise is essentially indistinguishable from catarrhal jaundice or liver atrophy from other causes

Miscellaneous Conditions

Suppurative Pylephlebitis

This condition usually arises from ulcerative lesions of the gastro intestinal tract most commonly appendicitis The suppurative process may involve the portal vein as well as its mesenteric tributaries and branches within the liver itself which is usually enlarged with multiple abscess formation

The clinical picture is that of generalized sepsis with chills and intermittent fever Abdominal pain is always present and is frequently followed by abdominal distention Severe gastro-intestinal hemorrhage may terminate the course Transient jaundice is often present ranging from mild to moderate in intensity

Any patient with an initial history of an acute abdominal episode or/and laparotomy a clinical picture of sepsis with jaundice and enlarged tender liver should arouse the suspicion of suppurative pylephlebitis

Pyogenic and Amebic Abscesses of the Liver

The multiple pyogenic abscesses of the liver arising in the course of suppurative pylephlebitis present a clinical picture similar to the one described above The fever is of the so called picket fence type and is generally accompanied by daily chills The pain is usually experienced in the right upper quadrant of the abdomen is more or less constant and present in the majority of cases It may radiate from the right hypochondrium to the right shoulder possibly owing to irritation of the phrenic nerve or diaphragmatic pleurisy The patient may complain of pain in the right lower chest on inspiration Tenderness over the liver area and hepatic enlargement are frequently present Jaundice occurs in from 8 per cent to 25 per cent of cases Icterus is usually a late serious sign Ascites is rare

In amebic abscess of the liver jaundice is rare and when present mild

Liver function tests give positive results The *process may progress* into the stage of acute liver atrophy, and jaundice may be prolonged for many weeks, *with recovery slow Ascites* occasionally develops Most of the fatalities occur within the first six weeks

Neocinchophen seems to be far less toxic both clinically and experimentally.

Sulfonamides

Jaundice complicating treatment with sulfonamides (particularly sulfanilamide) is more common than with cinchophen or arsphenamine There may be a prominent hemolytic factor with outspoken anemia and increased fecal urobilinogen The most common type of jaundice is that due primarily to liver injury, and here icterus develops after the drug has been taken for a week or two or even after the chemotherapy has been terminated It occasionally comes *on after a small total dose The clinical course is very similar to* that of catarrhal jaundice The onset is insidious The liver may be enlarged, and *liver* function tests *show functional impairment The* blood cholesterol and cholesterol esters are depressed The patient recovers if the drug is stopped Persistence of chemotherapy is dangerous, for severe hepatic injury or acute liver atrophy with lethal outcome occur In these fatal cases there is every reason to believe that there was previous liver damage, as for example, in the presence of severe infections or toxemias or when the drug was given to a patient also receiving antisyphilitic treatment When associated with exfoliative types of dermatitis the cases of sulfanilamide poisoning are indistinguishable clinically from arsphenamine poisoning

Mushroom Poisoning

Amanita phalloides is the poisonous mushroom in America that causes jaundice The pathological lesion in the liver consists essentially of diffuse, acute, *fatty changes In addition* there are acute hemorrhagic gastroenteritis and myocardial degeneration Jaundice develops in two or three days after *ingestion of the mushroom,* which causes colicky diarrhea and vomiting as the initial symptom Prostration is marked, the liver becomes enlarged *and tender* and the spleen palpable The urine contains casts and albumin and anemia develops

ticularly in the absence of symptoms of chronic active hepatitis since it is frequently discovered for prolonged periods in patients who have apparently completely recovered from the acute attack If other evidence of activity is not present the exercise-tolerance test must be employed before a decision can be made that the process is still active) Inflammatory reaction in the periportal spaces can be *seen in liver biopsy specimens*

In these patients nonvisualization of the gall bladder by roentgen studies may lead to an erroneous diagnosis of chronic cholecystitis This error becomes obvious when with eventual recovery normal concentration of the dye in the gall bladder can be demonstrated The recovery may not take place for a number of months or even a year if not longer Cirrhosis as a sequela is believed to be rare The diagnosis of chronic or relapsing hepatitis in the presence of jaundice should not be difficult if the past history is kept in mind Other forms of jaundice (obstructive spirochetal hemolytic) must be ruled out This subject is covered in other parts of this book

Repeated periods of gradual destruction of liver parenchyma and incidental fibrosis may be accompanied by the process of repair or regeneration Ultimately complete degeneration of the remaining liver cells may take place and cholemia or some intercurrent infection and death supervene The process of a chronic progressive destructive lesion of the liver combined with reparative activity and laying down of connective tissue is known to clinicians under the term of cirrhosis

The chronic form of hepatitis is in a sense synonymous with cirrhosis However this does not indicate that all types of cirrhosis follow hepatitis many are probably related to other factors The course of the disease when hepatic degeneration is recurrent and *associated with regeneration* has *been described* under *many titles* multiple nodular hyperplasia following acute atrophy toxic cirrhosis chronic liver atrophy subacute diffuse hepatitis nodular sclerosis of the liver—chronic infectious jaundice All these terms are confusing and often do not have any direct bearing upon the clinical problem envisaged in practical terms of diagnosis and treatment The clinical diagnosis of types of cirrhosis is in certain aspects and in most circumstances (except for biliary and metabolic cirrhosis) a purely academic problem and is extremely difficult There are certain clinical features common to all chronic forms of the

PARENCHYMATOUS JAUNDICE (CONTINUED)—CHRONIC HEPATITIS CARCINOMA

THE chronic types of jaundice and hepatitis are not well under stood and their etiology is often obscure In the description of catar rhal or infectious jaundice mention was made of cases in which the condition progresses to a subacute or chronic form Also in instances of toxic jaundice due to hepatotoxic chemicals a chronic course may follow In such patients jaundice may last for a number of months and then sometimes suddenly disappear The liver, how ever remains enlarged and rather hard and icterus may recur from time to time

The recurrent or chronic forms of hepatitis following the acute stage of an infectious process in the liver with or without jaundice have received special attention during World War II So far it has not been possible to ascertain accurately the true incidence of this condition but it is probably more common than generally sus pected There is usually a history of an acute febrile illness con sistent with acute hepatitis or frank jaundice in the past followed by partial recovery Many symptoms are rather vague and not par ticularly diagnostic such as lassitude fatigue and mental depression loss of weight or failure to gain weight Complaint of soreness aching heaviness or fullness in the right upper quadrant right lower chest and right lumbar region are more helpful There may be fever Of course the presence of jaundice observed in some patients materially helps in providing the clue as to the diagnosis The liver is always enlarged and may be tender Cervical lymphadenopathy may be discovered on careful physical examination Ascites and spider angiomatas are present in a few patients The laboratory tests show hepatic functional impairment (Elevated blood bilirubin as the only positive laboratory finding is not sufficient evidence par

postarsphenamine jaundice but in those that do there is very little doubt about the heavy metal being the etiological factor the same reasoning applies in the case of alcohol Others maintain that not alcohol *per se*, but rather the associated restricted dietary habits are of consequence thus making cirrhosis a deficiency disease An inquiry into the dietary habits of many chronic alcoholics with or

TABLE XXIII

PORTAL CIRRHOSIS
Clinical Features—Portal cirrhosis represents the most common type of chronic hepatitis It may exist for a number of years without causing symptoms (compensated stage) In the differential diagnosis of jaundice only the decompensated stage of the disease need be considered Sudden hematemesis due to bleeding from the oesophageal varices may usher in the clinical course of the disease Lassitude weakness impotence abdominal discomfort or pain nausea and vomiting and swelling of the abdomen are among the chief complaints Many cirrhotic patients are also chronic alcoholics The outstanding signs are ascites dependent edema enlarged liver and spleen spider angiomas and dilated veins over the abdomen Ascites is the most frequent and most characteristic sign The liver may not be palpable in the far advanced atrophic stage Arterial spiders are observed in about 50 per cent of the cases Jaundice occurs at some time or another in at least half the patients Although the evidence of collateral circulation is frequently found in dilated veins over the abdomen and chest caput medusae is exceedingly rare Irregular low grade fever is a fairly common manifestation
Laboratory Findings—Anemia is rather common and in some instances is of a macrocytic type Some patients have leucopenia with relative lymphocytosis and thrombocytopenia Bilirubinemia is from slight to moderate with positive direct van den Bergh reaction Liver function tests show impairment The plasma proteins are depressed with inversion of the normal albumin/globulin ratio X ray studies may demonstrate oesophageal varices
Differential Diagnosis—In a characteristic case presenting ascites palpable liver and spleen evidence of collateral circulation over the abdomen and spider angiomas the diagnosis of portal cirrhosis can easily be made Some jaundiced cirrhotics have clay-colored stools and dark colored urine simulating obstruction Occasionally attacks of abdominal pain colicky in nature may raise the suspicion of a common duct stone The liver function tests fail to demonstrate any impairment in the early stages of obstructive jaundice The Takata Ara test is frequently positive in cirrhosis

disease In all of them intercurrent attacks of icterus simulating simple catarrhal jaundice may occur The important thing is to establish that the patient does have cirrhosis and to determine if possible whether he suffers from an active degenerative process (decompensated cirrhosis) or has an inactive scarring process of the liver (compensated cirrhosis) In the latter case cirrhosis is fre quently an incidental finding at autopsy whereas in the former instance the patient usually has symptoms and seeks medical advice

In this book only two types of cirrhosis will be discussed at any length portal or Laennec s cirrhosis and cirrhosis secondary to chronic biliary obstruction Portal cirrhosis is the type most com monly encountered and therefore its consideration has great prac tical import Cirrhosis secondary to chronic biliary obstruction is relatively rare as compared with the former type but its recognition is important In addition a few remarks will be made regarding some of the other rarer types of cirrhosis

Portal Cirrhosis

There have been differences of opinion concerning the definition of Laennec s cirrhosis and portal cirrhosis as seen on pathological examination However here we shall make no distinction between the terms portal cirrhosis or Laennec s cirrhosis of the liver

The etiology of this disease has not as yet been definitely established although the more recent investigations have shed some light on the possible causative or at least precipitating factors

The relation of alcoholism to cirrhosis has been noted for some time Many cirrhotic patients give a definite and unequivocal his tory of alcoholism In one large series of cases alcohol was the most frequently encountered contributing etiologic factor Yet cirrhosis develops in only a small percentage of individuals addicted to alco hol and it occurs also in nonalcoholics Moreover it has not been possible to produce cirrhosis in experimental animals on administra tion of alcohol without the addition of other toxic substances

It is felt that some people may be more susceptible to the influ ence of alcohol on the liver than others the problem of selective susceptibility being very much of the same order as in regard to other hepatotoxic agents as for example arsphenamine As Licht man points out only a few patients treated with arsenicals develop

the above symptoms or in their absence the chief complaint may be related to abdominal pain either generalized or localized to the right upper quadrant and epigastrium Occasionally attacks of abdominal pain because of their severity and frequent association of jaundice may raise the suspicion of common duct stone Irregular, low grade fever is also a fairly common early manifestation This

TABLE XXIV

INITIAL SYMPTOMS AND SIGNS OF LAENNEC S CIRRHOSIS IN 386 PATIENTS

Symptoms	*Number of Cases*	*Per Cent of Cases*
Swollen abdomen	107	27 7
Abdominal pain	48	12 4
Hematemesis	39	10 1
Edema of lower extremities	36	9 6
Jaund ce	34	8 8
Nausea and vomiting	29	7 5
Weakness	22	5 7
Abdominal distress	17	
Bleeding epistaxis	15	
Diarrhea	14	
Anorexia	9	
We ght loss	7	
Dyspnea (in absence of ascites)	6	
Abdominal mass (liver or spleen)	5	
Melena (without hematemes s)	4	
Cough	4	

From Ratnoff and Patek Medicine 24 207 1942

may be due to destruction of liver parenchyma and not a complicating infectious disease Jaundice nausea and vomiting are among other initial symptoms frequently encountered Later weakness appears with loss of weight, particularly apparent over the upper extremities

The outstanding signs of portal cirrhosis in the decompensated stage are ascites with or without dependent edema palpable liver and spleen jaundice, telangiectasia or spider angiomatas and dilated veins over the abdomen To these may be added varicose veins with or without pigmentation of the skin over the shins scanty body hair liver palms signs of peripheral neuritis the characteristic caput medusae, and hydrothorax

without liver disease will reveal that their intake of food is deficient *in many respects* Experimental evidence supporting the deficiency theory has been presented in a convincing fashion In experimental animals cirrhotic lesions have been produced with a low protein low vitamin (vitamin B) high fat diet It is felt that the marked incidence of cirrhosis in North China is related to malnutrition The modern treatment of both acute and chronic forms of hepatitis is based on these concepts and has proved to be more successful than the hitherto accepted practice

Pathologically cirrhosis is essentially a chronic progressive diffuse hepatitis The three fundamental pathological changes are those of necrosis regeneration and sclerosis (laying down and contraction of connective tissue) It may be regarded as a chronic inflammatory process that is progressive and proliferative in nature rather than exudative The areas of parenchymal necrosis are replaced by fibrous tissue Both destructive and fibrotic processes may possibly be the result of the same noxious influences on the parenchymal and inter stitial tissues of the liver Side by side with destructive and fibrotic reactions compensatory hypertrophy and regeneration take place At first the hypertrophied liver may be normal or increased in size and weight (hypertrophic stage) Later with the destruction racing ahead of regeneration and from the contraction of the mass of fibrous tissue the liver begins to shrink in size becoming smaller than normal and therefore no longer palpable (atrophic stage) From the clinical point of view the cirrhotic process may be considered to be in a compensated stage in the absence of symptoms (latent cirrhosis) or in the stage of decompensation when a certain trend of signs and symptoms begins to develop It is the latter stage that concerns us here

The outstanding symptoms of the decompensated stage are nausea vomiting hematemesis and abdominal pain Impotence in the male is also a common symptom In a few patients this rather than any other disturbance may be the reason for medical consultation

Among the initial complaints probably the most common first symptom is the insidious onset of swelling of the abdomen usually painless but at times accompanied by either abdominal pain or distress Sudden hematemesis due to bleeding from the oesophageal varices may usher in the clinical course of the disease Along with

TABLE XXV

PHYSICAL SIGNS OF LAENNEC'S CIRRHOSIS IN 386 PATIENTS

Physical Signs	*Number of Cases*	*Per Cent of Cases*
Ascites	301	78 0
Palpable liver	291	75 4
Jaundice	252	65 3
Edema	236	61 1
Palpable spleen	170	44 0
Hemorrhoids	105	27 2
Fever without apparent cause	93	24 5
Dilated veins	91	23 6
Telangiectasis	67	17 4
Spider angiomata	58	15 0
Peripheral neuritis	40	10 4
Varicose veins	37	9 6
Hypoflexia	32	8 3
Absent deep reflexes	29	7 5
Hydrothorax	25	6 5
Scanty body hair	25	6 5
Pigmentation over shins	22	5 7
Clubbed fingers or curved fingernails	21	5 4
Cyanosis	19	
Umbilical hernia	17	
'Liver palms	16	
Inguinal hernia	14	
Hyperactive deep reflexes	14	
Generalized pigmentation	10	
Clay colored stools	7	
Toxic delirium	6	
Tremor	6	
Hypesthesia	5	
Caput medusae	4	

From Ratnoff and Patek Medicine 21 207 1942

In a characteristic case presenting some of the cardinal signs described above such as ascites jaundice palpable liver and spleen, evidence of collateral circulation over the abdomen and spider angiomata the diagnosis of portal cirrhosis can easily be made However, in some cases a recurrence to special procedures has to be made Among these the most valuable is peritoneoscopy It permits direct visual inspection of the liver and removal of a specimen for

Ascites is the most frequent and most characteristic sign Almost as frequent in appearance as ascites is *edema* usually of the lower extremities Jaundice occurs at some time or another in at least half the cirrhotic patients Usually it is relatively mild or moderate in degree but occasionally it may be severe Icterus is ordinarily of serious prognostic significance

The *pathogenesis of jaundice in cirrhosis* has not been definitely established and is not clearly understood but it is probably not of hemolytic origin The fragility of erythrocytes to hypotonic salt solution is within normal limits The study of autopsy material fails to reveal any correlation between necrosis in the liver cells and the presence of jaundice Of course the absence of necrosis in the liver does not exclude functional derangement

A majority of cirrhosis patients have palpable livers The palpability is dependent upon not only the size of the liver but also its density and the resistance of the abdomen to palpation Marked ascites may make the demonstration of hepatomegaly difficult In the presence of fluid the organ may be felt by *ballottement* or after abdominal paracentesis In the later stages the liver becomes contracted and no longer palpable *A palpable spleen is also a frequent finding* The enlargement of the spleen is common at autopsy whether or not this organ is palpable clinically

Dilated veins apparent over the abdomen and chest frequently serve as evidence of collateral circulation between the portal and *systemic circulation* but the characteristic caput medusae around the umbilicus is encountered in only a small proportion of patients The spider angiomatas and telangiectasia should be looked for over the face and chest

Among the less commonly recognized physical signs are the so-called *liver palms* and scanty body hair The former is represented by erythema of the palms with pink and flushed appearance of the thenar and hypothenar eminences It is not necessarily *specific for* cirrhosis and is observed in other conditions such as rheumatoid arthritis * In addition to ascites hydrothorax may be present

The *prognosis is grave in cirrhosis* of the liver once signs of decompensation have appeared such as ascites jaundice and hematemesis

* The sign is observed in many *unrelated diseases*, which however have a common denominator of protein deficiency and hypoalbuminemia

in the large bile ducts fibrosis spreads from the ducts to surround the liver lobules and even invades them to appear between the individual liver cells Parenchymal degeneration supervenes and actual necrosis may be present The liver may assume a granular or nodular appearance The following etiological agents responsible for obstruction were found in a series of 21 cases among 244 patients with obstructive jaundice (Gibson and Robertson)

Postcholecystectomy stricture	10
Common duct stone	6
Carcinoma of the ampulla of Vater	2
Carcinoma of the gall bladder (with invasion of the common duct)	1
Carcinoma of the head of the pancreas	1
Carcinoma of the stomach (with invasion of the common duct)	1

TABLE XXVI

CLINICAL DIFFERENTIATION BETWEEN PORTAL AND BILIARY CIRRHOSIS

	Portal Cirrhosis	*Biliary Cirrhosis*
Chills and fever	low grade fever is often present, chills are not a prominent feature (particularly in the absence of intercurrent infection)	chills and fever are characteristic
Evidence of biliary obstruction	absent	present
Jaundice	commonly not very marked present as an initial or terminal sign	variable but frequently more marked, more constant finding, more continuous
Abdominal pain	may be present, not characteristic	attacks of biliary colic not uncommon
Ascites and hematemesis	common as either initial or terminal events	less common, usually appear only after a period of prolonged jaundice (for months)
Hepatic enlargement	commonly present may be absent in terminal stage	more marked
Splenic enlargement	common	less common
Caput medusae	more common	extremely rare
Clubbing of the fingers	rare	more common

biopsy and the exclusion of such commonly associated conditions as tuberculous peritonitis and malignancy of the liver To rule out the latter possibility, the roentgen visualization of the general structure of the liver by means of *thorotrast (thorium dioxide)* injected intravenously may be of great value

A few jaundiced cirrhotics have clay-colored stools and dark colored urine, simulating obstruction The cephalin cholesterol flocculation and Takata Ara tests are usually positive, and various liver function tests such as a galactose tolerance and hippuric acid synthesis show hepatic functional impairment The plasma proteins are depressed with inversion of the normal albumin/globulin ratio due to depression of the albumin fraction with or without elevation of globulin

Banti s syndrome particularly in the later stages associated with ascites jaundice, and sometimes fever, is indistinguishable clinically from portal cirrhosis In fact the author sees no reason from the *practical point of view for taking pains in differentiating between* the two conditions

Although hemochromatosis may simulate ordinary portal cirrhosis in the compensated state, it need not be considered in the differential diagnosis of jaundice as icterus is not a feature of this disease

Cirrhosis from Biliary Obstruction

(Biliary Cirrhosis, Obstructive Biliary Cirrhosis)

This condition results from long standing obstruction of the extra hepatic biliary tract This type of cirrhosis is *comparatively rare*, *as* in man mechanical biliary occlusion seldom results in the clinical picture of cirrhosis although fibrosis may be detected on microscopic examination *The ability to recognize this condition as early as possible in the course of the disease is important because the removal of the primary causative factor (obstruction) can bring about recovery in those patients who have not been allowed to go on long enough to develop irreparable liver damage* Unique contributions to our understanding of this entity have recently been made

As a result of prolonged obstruction associated with infection

to xanthomatous changes in the larger bile ducts The latter may conceivably give rise to biliary cirrhosis and for this reason the disease is often referred to as biliary xanthomatous cirrhosis Thus jaundice may be attributed either to parenchymal liver involvement *or mechanical factors or both*

The liver and spleen are palpable Icterus may be marked and long lasting and is frequently the initial symptom Jaundice of unusually long duration may help to differentiate this condition from ordinary portal cirrhosis The associated xanthomatous lesions of the skin present in some patients help to distinguish it from both portal and biliary cirrhosis Hypercholesterolemia is common to all three disease entities However this finding is subject to change with relief of biliary obstruction in ordinary biliary cirrhosis whereas in the case of xanthomatous cirrhosis the level of blood cholesterol remains constantly elevated At the same time the cholesterol ester fraction may be low in the presence of severe hepatic damage In the absence of characteristic cutaneous lesions of xanthomatosis the diagnosis can be established only with liver biopsy which should reveal the characteristic foam cells scattered *throughout the liver substance*

Carcinoma of the Liver

Primary Cancer of the Liver

This is a difficult condition to diagnose except in a well advanced or terminal stage of the disease Although one of the more rare diseases of the liver it probably is not as rare as is generally thought and the diagnosis is frequently missed ante mortem Keeping in mind certain salient features of the clinical course would help one materially in making the correct diagnosis on a patient who presents certain suggestive symptoms and signs

A carcinomatous process may originate either in the parenchymal liver cells or the bile ducts The malignancy of the former type far outnumbers the latter The condition may be found at any age but *it is predominantly a disease of middle life most often found be*tween the ages of 50 and 60 and occurring more often in males than in females The reason for this is apparent the most important coexisting or perhaps even contributing factor in hepatic carcinoma

Among other and rarer causes congenital stenosis of the biliary tract and *parasites impacted in the* common duct may be mentioned Both infectious and obstructive factors are present although all signs of infection may have long disappeared Bouts of chills and fever indicate the persistence and reactivation of the infection There is often a history of intermittent jaundice particularly in patients with benign obstruction While the liver is enlarged *the spleen is* not as commonly palpable Jaundice is marked but may vary in *accordance with the degree* and permanence of obstruction until the progression of the hepatic lesion becomes a determining factor Ascites may supervene and occasionally there is hematemesis from ruptured oesophageal varices Venous collaterals sometimes develop but caput medusae is extremely rare Clubbing of the fingers is common The liver function tests show functional impairment

Non Obstructive Biliary Cirrhosis

Non obstructive or hypertrophic biliary cirrhosis (of Hanot) is an entirely different condition and may not represent a pathological entity It is very rare the author has never seen a case According to the literature this type of cirrhosis is characterized by long stand ing jaundice periodic febrile attacks of abdominal pain and hepato splenomegaly in the relative absence of ascites The extrahepatic bile *channels are grossly patent* and histologically the cirrhosis is intra lobular The disease appears to be most common in young males

Xanthomatous Cirrhosis

Primary or essential xanthomatosis constitutes a very interesting group of different clinical manifestations of disturbed cholesterol metabolism attributable to no determined cause Practically every organ of the body such as the integument bones liver spleen *heart (coronary arteries) and others* may be involved The clinical picture and the name of the disease depend upon the organ or organs in which the process is most extensive When liver and spleen are primarily involved the condition is known as xanthomatous cirrhosis and may be easily confused with portal or *biliary cirrhosis*

The pathological process consists essentially of infiltration of the liver with the nests of characteristic xanthoma cells (foam *cells)* secondary changes of cirrhosis and partial biliary obstruction due

TABLE XXVIII

PRIMARY CARCINOMA OF THE LIVER
Clinical Features—Primary carcinoma of the liver is an uncommon con dition The disease is marked by an insidious onset but once well estab lished it develops rapidly The characteristic symptoms and signs are weight loss abdominal pain jaundice ascites a palpable hard nodular liver and a progressively down hill course The most characteristic sign is the enlarged firm or stony hard irregular nodular liver which is only slightly tender or not tender at all The spleen may be palpable and ascites is common Unexplained fever of mild to moderate degree may arouse the suspicion of an infectious process Most commonly carcinoma develops in a cirrhotic liver and therefore there may be a history of portal cirrhosis antedating by a number of years the terminal illness
Laboratory Findings—Anemia is commonly present Liver function tests show surprisingly l ttle impairment despite marked malignant involve ment Ascitic fluid may be bloody
D fferential Diagnosis—Clinical diagnosis is d fficult in the early stage In patients known to have cirrhos s a suspicion of malignant neoplasm is justifiable with the advent of such symptoms and signs as a progressively downhill course an increase in size hardness irregularity and nodu *larity of the liver recovery of bloody ascitic fluid an otherwise unexplain* able fever and the absence of any demonstrable primary tumor elsewhere

frequently encountered in malignancy than in cirrhosis but is com monly absent in the initial stages of the disease It varies in intensity and usually is not very marked at any time Hemorrhagic phenomena are comparatively rare hematemesis may occur from oesophageal varices in advanced cases or near death On the other hand con cealed bleeding into the peritoneal cavity from the surface of the liver is not unusual

The most characteristic sign is the enlarged firm to stony hard irregular nodular liver which is only slightly tender or not tender at all The spleen may be palpable but infrequently so and then usually in cases associated with cirrhosis A more constant finding is ascites It occurs in 45 to 60 per cent of the cases and on abdom inal paracentesis the ascitic fluid may be found to be bloody in appearance (the demonstration of malignant cells in ascitic fluid is a rarity and cannot therefore be depended upon for diagnosis) Ascites is usually associated with pre existing cirrhotic changes or

is cirrhosis, a disease more prevalent among males (sex ratio being 3 to 1)

The occurrence of multiple carcinomatous nodules in the affected liver raises the question whether they represent metastatic lesions or multiple foci of primary cancerous degeneration At any rate, whereas regional or intrahepatic metastases are probably common, metastases to distant organs are rare

TABLE XXVII

ANALYSIS OF SYMPTOMS AND SIGNS IN 40 CASES OF PRIMARY CARCINOMA OF THE LIVER

Symptoms and Signs	*Number of Cases*	*Per Cent of Cases*
Abdominal mass	31	77 5
Abdominal pain	29	72 5
Jaundice	24	60 0
Ascites	24	60 0
Weight loss	21	52 5
Peripheral edema (legs)	17	42 5
History of alcoholism	9	22 5
Gross bleeding (recurrent epistaxis, hematemesis or melena)	7	17 5

After Wilbur Wood and Willett Ann Int. Med 20 453 1944

The characteristic symptoms and signs are the complaints of weight loss and abdominal pain jaundice, ascites and a palpable, hard nodular liver

The symptoms that usually force the patient to seek medical attention are pain and weakness The pain is usually localized to the right upper quadrant of the abdomen and/or back and is a more frequent and constant complaint than in portal cirrhosis Apart from pain, the gastro-intestinal symptoms are not a conspicuous feature and are vague Pain itself is not severe except terminally, and is usually dull and aching in character Weakness may be an initial or associated symptom rapidly growing more marked and finally forcing the patient to give up his daily routine Loss of weight is not prominent at first but becomes marked in the advanced or terminal stages of the disease History of alcoholism is frequently elicited (remember the relation of incidence of cirrhosis to hepatic cancer) Jaundice is present in 50 to 60 per cent of cases It is more

BIBLIOGRAPHY

Ashe W F Pratt Thomas H R and Kumpe *Medicine* 20 145 1941
Barker N H Capps R B and Allen F W *J A M A* 128 997 1945 ibid 129 653 1945
Barth C and Alexenco W *Klin Wchnschr* 20 102 1941
Beeson P B *J A M A* 121 1332 1943
Bertucci E A Jr *Am J Med Sci* 209 86 1945
Bloomfield A L *Am J Med Sci* 195 429 1938
Bodansky A *Enzymologia* 3 258 1937
Bull U S Army M Dept Nov 1943 No 70 p 4
Bull U S Army Dept Nov 1944 No 82 p 7
Caravati C M *South M J* 37 251 1944
Cockayne E A *Quart J Med* 6 1 1912
Durand J A *New Orleans M & S J* 94 341 1912
Editorial *J A M A* 119 1110 1942
Editorial *J A M A* 123 636 1943
Editorial *Brit M J* 2 680 1943
Eppinger H *Verh d Deutsch Ges f inn Med* 34 15 1922
Eppinger H *Die Leberkrankheiten* Wien Julius Springer 1937
Findlay G M and Martin N H *Lancet* 1 678 1943
Finks R M and Blumberg R W *Arch Int Med* 75 102 1945
Fleming R G and Snell A M *Am J Digest Dis and Nutr* 9 115 1942
Ford J C *Lancet* 1 675 1943
Fox J P Manso C Penna H A and Para M *Am J Hyg* 36 68 1942
Frerichs F T *Klinik d Leberkrankheiten* Braunschweig Vieweg u Sohn 1858
Gaskell J F *J Path and Bact* 36 257 1933
Gibson W R and Robertson H E *Arch Path* 28 37 1939
Greene J M *Internat Abstr Surg* 69 231 1939
Greene C H *Arch Int Med* 71 563 1943
Greene C H and Farrell E *Arch Int Med* 65 847 1940
Grossman C M and Saward E W *New England J Med* 234 181 1946
Gyorgy P *Am J Clin Path* 14 67 1944
Gyorgy P and Goldblatt N *J Exper Med* 70 185 1939 ibid 75 355 1942
Hanger M D and Gutman A B *J A M A* 115 263 1940
Hartfall S J and Garland H G *Lancet* 230 1459 1936
Havens W P Jr *Proc Soc Exper Biol & Med* 58 203 1945
Havens W P Jr Paul J R and Van Rooyen C E *Lancet* 1 202 1945
Havens W P Jr Ward R Drill V A and Paul J R *Proc Soc Exper Biol & Med* 57 206 1944
Herxheimer G *Beitr und path Anat* 72 56 1923
Herxheimer G and Gerlach W *Beitr z path Anat U Z allg Path* 68 93 1921
Himsworth H P and Glynn L E *Lancet* 1 457 1944

thrombosis of the portal vein Associated dependent edema of the legs is a frequent occurrence

Unexplained fever of mild to moderate degree, and sometimes with septic swings may arouse the suspicion of an infectious process On the other hand, hypothermia has been reported, but this must be a very rare occurrence

The laboratory studies reveal albuminuria, bilirubinuria, and slight to moderate anemia, at times associated with slight or moderate leucocytosis The icterus index may be as low as 10 or as high as 200 In jaundiced cases it is more commonly in the range between 20 and 50 units Liver function tests may reveal functional impairment, but it is surprising how frequently this evidence is lacking even in advanced cases

Clinical diagnosis is difficult in the early stages A typical picture is that of a middle aged male complaining of mild or moderately severe abdominal pain with a large, hard, irregular, and nodular liver, mild to moderate jaundice, and ascites with an otherwise unexplainable fever and the absence of any demonstrable primary tumor elsewhere Gradual and often rapid increase in size, irregularity, and nodularity of the liver, recovery of bloody ascitic fluid and a rapid decline in health would all tend to support the belief that one is dealing with a case of primary hepatic cancer The proof will rest with inspection of the liver during laparotomy or on peritoneoscopy and microscopic examination of biopsy material

Matastatic Cancer of the Liver

Jaundice is either absent or *slight in the majority* of cases of metastatic carcinoma of the liver The condition may be suspected in a patient with rapid enlargement of the liver presenting a nodular surface, and extreme cachexia with a generally downhill course Jaundice, ascites, and fever lend weight to the suspicion but the diagnosis again can be proved only by direct inspection and biopsy The demonstration of a primary growth is often very difficult The cases of liver carcinoma are more frequently metastatic than primary in origin

Occasionally jaundice is very marked due to complete *obstruction* of major hepatic ducts by the metastatic involvement of the hilar lymph nodes or by the metastatic *nodules in parts* of the liver adjacent to the hilum hepatis

BIBLIOGRAPHY

Ashe W F Pratt Thomas H R and Kumpe *Medicine* 20 145 1941
Barker N H Capps R B and Allen F W *J A M A* 128 997 1945 ibid 129 653 1915
Barth C and Alexenco W *Kl n W chnscher* 20 102 1941
Beeson P B *J A M A* 121 1332 1943
Bertucci E A Jr *Am J Med Sci* 209 86 1945
Bloomfield A L *Am J Med Sci* 195 429 1938
Bodansky A i *Enzymologia* 3 258 1937
Bull U S Army M Dept Nov 1943 No 70 p 4
Bull U S Army Dept Nov 1944 No 82 p 7
Caravati C M *South M J* 37 251 1944
Cockayne E A *Quart J Med* 6 1 1912
Durand J A *New Orleans M & S J* 94 341 1942
Editorial *J A M A* 119 1110 1942
Editorial *J A M A* 123 636 1943
Editorial *Brit M J* 2 680 1943
Eppinger H *Verh d Deutsch Ges f inn Med* 34 15 1922
Eppinger H *Die Leberkrankheiten* Wien Julius Springer 1937
Findlay G M and Martin N H *Lancet* 1 678 1943
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Fleming, R G and Snell A M *Am J Digest Dis and Nutr* 9 115 1942
Ford J C *Lancet* 1 675 1943
Fox J P Manso C Penna H A and Para M *Am J Hyg* 36 68 1942
Frerichs F T *Klinik d Leberkrankheiten* Braunschweig Vieweg u Sohn 1858
Gaskell J F *J Path and Bact* 36 257 1933
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Greene C H *Arch Int Med* 71 563 1943
Greene C H and Farrell E *Arch Int Med* 65 847 1940
Grossman C M and Saward E W *New England J Med* 234 181 1946
Gyorgy P *Am J Clin Path* 14 67 1944
Gyorgy P and Goldblatt N *J Exper Med* 70 185 1939 ibid 75 355 1942
Hanger M D and Gutman A B *J A M A* 115 263 1940
Hartfall S J and Garland H G *Lancet* 230 1459 1936
Havens W P Jr *Proc Soc Exper Biol & Med* 58 203 1945
Havens W P Jr Paul J R and Van Rooyen C E *Lancet* 1 202 1945
Havens W P Jr Ward R Drill V A and Paul J R *Proc Soc Exper Biol & Med* 57 206 1944
Herxheimer G *Beitr und path Anat* 72 56 1923
Herxheimer G and Gerlach W *Beitr z path Anat U Z allg Path*, 68 93 1921
Himsworth H P and Glynn L E *Lancet* 1 457 1944

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BIBLIOGRAPHY

Ashe W F Pratt Thomas H R and Kumpe *Medicine* 20 145 1941
Barker N H Capps R B and Allen F W *J A M A* 128 997 1945 ibid 129 653 1945
Barth C and Alexenco W *Klin Wchnschr* 20 102 1941
Beeson P B *J A M A* 121 1332 1943
Bertucci E A Jr *Am J Med Sci* 209 86 1945
Bloomfield A L *Am J Med Sci* 195 429 1938
Bodansky A *Enzymologia* 3 258 1937
Bull U S Army M Dept Nov 1943 No 70 p 4
Bull U S Army Dept Nov 1944 No 82 p 7
Caravati C M *South M J* 37 251 1944
Cockayne E A *Quart J Med* 6 1 1912
Durand J A *New Orleans M & S J* 94 311 1942
Editorial *J A M A* 119 1110 1942
Editorial *J A M A* 123 636 1943
Editorial *Brit M J* 2 680 1943
Eppinger H *Verh d Deutsch Ges f inn Med* 34 15 1922
Eppinger H *Die Leberkrankheiten* Wien Julius Springer 1937
Findlay G M and Martin N H *Lancet* 1 678 1943
Finks R M and Blumberg R W *Arch Int Med* 75 102 1945
Fleming R G and Snell A M *Am J Digest Dis and Nutr* 9 115 1942
Ford J C *Lancet* 1 675 1913
Fox J P Manso C Penna H A and Para M *Am J Hyg* 36 68 1942
Frerichs F T *Klinik d Leberkrankheiten* Braunschweig Vieweg u Sohn 1858
Gaskell J F *J Path and Bact* 36 257 1933
Gibson W R and Robertson H E *Arch Path* 28 37 1939
Greene J M *Internat Abstr Surg* 69 231 1939
Greene C H *Arch Int Med* 71 563 1943
Greene C H and Farrell E *Arch Int Med* 65 847 1940
Grossman C M and Saward E W *New England J Med* 234 181 1946
Gyorgy P *Am J Clin Path* 14 67 1944
Gyorgy P and Goldblatt N *J Exper Med* 70 185 1939 ibid 75 355 1942
Hanger M D and Gutman A B *J A M A* 115 263 1940
Hartfall S J and Garland H G *Lancet* 230 1459 1936
Havens W P Jr *Proc Soc Exper Biol & Med* 58 203 1945
Havens W P Jr Paul J R and Van Rooyen C E *Lancet* 1 202 1945
Havens W P Jr Ward R Drill V A and Paul J R *Proc Soc Exper Biol & Med* 57 206 1944
Herxheimer G *Beitr und path Anat* 72 56 1923
Herxheimer G and Gerlach W *Beitr z path Anat U Z allg Path* 68 93 1921
Himsworth H P and Glynn L E *Lancet* 1 457 1944

Hurst A F and Simpson C K *Guys Hosp Rep* 84 173 1934
Inada R J *Exper Med* 26 355 1917
Jolliffe N *Am J Med Sci* 186 640 1933
Klemperer P Killian J A and Heyd C G *Arch Path and Lab Med* 2 631 1926
Klotz O and Belt T H *Am J Path* 6 689 1930
Klotz O and Simpson W *Am J Trop Med* 7 271 1927
Kramer D W *Pennsylvania M J* 45 1298 1942
Leonard M F *Am J Med Sci* 208 461 1944
Lester B S Denison G A Posey L C and Tate G M *South M J* 35 325 1942
Lichtman S S *Diseases of the Liver Gall Bladder and Bile Ducts* Philadelphia Lea & Febiger 1942
McCallum F O and Bauer D J *Lancet* 1 6222 1944
McCallum F O and Bradley W H *Lancet* 2 228 1944
Martin L *Lancet* 2 480 1941
Mathews W R *Tr State Med J* 12 2511 1940
Medicine and the War *J A M A* 120 51 1943
Meyer K Eddie B and Stewart Anderson B *Am J Pub Health* 29 347 1939
Miller J and Rutherford A *Quart J Med* 17 81 1923
Minot G R and Jones C M *Boston M & S J* 189 531 1923
Moagland C L and Shank R E *J A M A* 130 615 1946
Morgan M T and Brown H C *Rep publ Hlth Med Subj Lond* No 42 1927
Morgan H V and Williamson D A J *Brit M J* 1 750 1943
Neefe J R and Stokes J Jr *J A M A* 128 1063 1945
Neefe J R Stokes J Jr Reinhold J G and Lukens F S W *J Clin Invest* 23 836 1944
Oliphant J W *Bull New York Acad Med* 20 429 1944
Oliphant J W Gilliam A G and Larsen C L *Pub Health Rep* 58 1233 1943
Ottenberg R and Spiegel R *Medicine* 22 27 1943
Paracelsus *Aur Theophr Paracelsae eremitae opera lat redd* tract 3 c.l 146 1585
Pass I J *Am J Path* 11 157 1935
Patek A J Jr *Proc Soc Exper Biol & Med* 37 329 1937
Paul J R Havens *W P* Jr Sabin A B and Philip C B *J A M A* 128 13 911 1945
Pickles W N *Brit M J* 1 944 1930
Polack E *Acta med ca Scand nav* 93 614 1938
Popper H and Wiedmann A *Ztschr f Klin Med* 131 258 1937
Priest R *Lancet* 2 124 1942
Rappaport E M *J A M A* 128 932 1945
Ratnoff O S and Patek A J Jr *Medicine* 21 207 1942
Reid J S and Holt R A *Virginia Med Month* 68 571 1941

Roholm K and Iversen P *Acta path et microbiol Scandinav* 16 427 1939
Roholm K and Krarup N B *Arch f Dermatol u Syph* 181 521 1940
Rokitansky C *Handbuch d spec path Anat* 3 313 1842
Rollerston H and McNee J W *Diseases of the Liver Gall Bladder and Bile Ducts* Philadelphia W B Saunders Company 1905
Ruge H *Arch f Dermat u Syph*, 153 578 1927
Sadusk J F Jr and Manahan C P *J A M A* 113 114 1939
Sager, R V *Arch Int Med* 57 666 1936
Saphirstein H *Urol & Cut Rev* 42 101 1938
Sawyer W A in Christian H A *Oxford Medicine* New York Oxford Univ Press vol 5 pt 3 p 723 Ch xxx 1940
Schultz E W *J Lab & Clin Med* 8 375 1923
Sheehan H L *Lancet* 2 8 1944
Snapper J *Chinese Lessons to Western Medicine* New York Interscience Publishers Inc 1941
Snell A M *Canad M A J* 37 318 1937
Snell A M *Calif & Western Med* 62 74 1945
Snell A M Wood D A and Meienberg L J *Gastroenterology* 5 241 1945
Soffer L J *Am J Syph Gonor & Ven Dis* 21 309 1937
Soper F L *J A M A* 118 374 1942
Steiner R E *Brit M J* 1 110 1944
Stokes A *Clinical Lectures on the Practice of Medicine* Dublin Famin & Company 1939
Stokes J Jr and Neefe J R *J A M A* 127 144 1945
Stokes A Ryle J A and Tytler W H *Lancet* 1 142 1917
Stowman K *J A M A* 128 185 1915
Thannhauser S J and Magendantz H *Ann Int Med* 11 1163 1938
Tiffany E J and Martorana N F *Am J Hyg* 36 195 1941
Turner R H Snavely J R Grossman E B Buchanan R N and Foster S O *Ann Int Med* 20 193 1944
Virchow R *Virchows Arch* 32 117 1865
Warthin A S *Am J Syph* 2 443 1918
Wilbur D L Wood D A and Willett F M *Ann Int Med* 20 453 1944
Wile U J and Sams *Am J Med Sci* 187 297 1934
Wilen C J Snavely J R and Bruno F E *New Orleans M & S J*, 94 338 1942
Wilenski A O *J Internat Coll Surg* 7 50 1944
Williams H *J A M A* 80 532 1923

OBSTRUCTIVE JAUNDICE

JAUNDICE has been referred to as a signpost on the biliary high way indicating that the route is blocked and a detour is being used for the bile to travel The reader has had the opportunity to see how this sign may denote obstruction anywhere between the liver cell and the terminal end of the common bile duct We have dis cussed in greater detail the forms of jaundice that originate proximal to or in the hepatic cell (hematogenous and hepatogenous icterus) We shall now devote our attention to the forms of jaundice that result from the disturbance distal to the parenchymal cell of the liver Here we are mostly concerned with the gross lesions producing mechanical biliary occlusion which are either congenital or ac quired The cases in the former group such as congenital atresia of the bile ducts are rare In the latter group are found biliary calculi stricture of the common duct carcinoma of the pancreas carcinoma of the extrahepatic ducts and of the gall bladder All these conditions can be classified as benign or malignant Such dif ferentiation has great practical importance and in many instances can be made on clinical grounds as the symptomatology and physical findings may be distinct in the two groups However there is some

TABLE XXIX

AGE DISTRIBUTION IN BENIGN AND MALIGNANT OBSTRUCTION

	Benign Obstruction	*Malignant Obstruction*
Age Limits	34 to 79	26 to 71
Average Age	55 5	48

From data by Meyer and Stegmann

overlapping so that the distinction between the malignant and benign types of obstruction cannot always be made clinically and errors can be expected to occur It is interesting to note that in one series of 62 patients no malignant cases were diagnosed as benign whereas 4 benign cases were diagnosed erroneously as malignant

The following analysis of symptoms and signs was made in the series of cases mentioned above

While dyspepsia before more concrete symptoms had begun was usually present only for a short time in the malignant group it had been present for years in the benign group *

In the malignant group 23 per cent of patients had sharp pains in the right upper quadrant of the abdomen 35 per cent complained of dull upper abdominal distress 18 per cent suffered from only vague abdominal discomfort while 23 per cent of patients had no pain among them cases of carcinoma of the pancreas and the gall bladder

Half the patients with benign obstruction had severe colicky pain while 40 per cent complained of only abdominal distress and 10 per cent had no pain at all

A history of significant loss of weight could be elicited from 65 per cent of patients in the malignant group but from only 18 per cent in the benign group Pruritis was encountered twice as frequently in the malignant group where the obstruction is more commonly complete Pruritis accompanied by factitious dermatitis was observed in the malignant group On the other hand chills fever and sweats were thrice as common in the benign group where associated infection of the biliary tract is more frequently encountered Jaundice had a greenish tinge more often in the malignant cases

History of alcoholism nausea and vomiting tenderness in the right upper quadrant of the abdomen and leucocytosis were found in almost equal proportions in the two groups The liver was palpable somewhat more frequently in the malignant than benign cases

Patients with malignant obstruction appeared to be more critically ill frequently wasted and somewhat apathetic while those

* An exception to this is presented by patients with carcinoma of the gall bladder who often give a history of cholelithiasis by many years antedating the development of a malignant process

with benign obstruction were better nourished, alert, complained loudly, and frequently required opiates for pain

A negative flat plate of the abdomen was found to be of no diagnostic importance as some stones do not visualize

Continued absence of urobilinogen in the urine and feces for 10 to 14 consecutive days was always found in association with malignant obstruction The reason for this is obvious from previous discussion Some of the findings above are summarized in the following table

TABLE XXX

THE INCIDENCE OF SYMPTOMS AND SIGNS IN BENIGN AND MALIGNANT OBSTRUCTION

	Finding	*Malignant Group %*	*Non Malignant Group %*
1	General attitude	rather apathetic	alert and complaining
2	Pruritis	41	21
3	Enlarged liver	82	68
4	Icterus	slowly mounting on high level	variable
5	Icterus above 100	75	21
6	History of sepsis	3	32
7	Loss of weight	65	18
8	No urobilin in urine	76	7
9	Acholic stools	76	7
10	Direct van den Bergh	83	21
11	Low galactose excretion	92	80
12	Ascending glucose tolerance curve	73	25
13	Morphine required for pain	0	50

Meyer and Sie gmann

The general experience is that gallstones are the most frequent cause of obstructive jaundice Carcinoma of the pancreas however, is a far more frequent cause than carcinoma of the liver, the bile ducts or the gall bladder

CHOLEDOCHOLITHIASIS

The common duct stone is usually secondary to cholecystitis or/and cholelithiasis Soft bile pigment stones may also form, secondary to persistent obstruction of the common duct in conditions such as pancreatitis and sphincteritis A less common contributory

cause are conditions of excessive blood destruction encountered in certain chronic hemolytic anemias (congenital hemolytic icterus sickle-cell disease) The excretion of an increased amount of bile pigment incidental to marked hemolysis leads to the precipitation of pigment calculi in the biliary tract

A stone formed in the gall bladder passes through the cystic duct and in 60 per cent of the cases settles in the terminal portion of the common duct About 10 per cent of common duct stones are strictly confined to the ampulla although some of them remain in the middle portion of the duct When a stone is too large to traverse the cystic duct it may be assumed that its nucleus made the journey and grew in size after having reached the ductus choledochus The calculi may be multiple

A stone or any other obstruction of the common bile duct is always followed either by dilatation of the duct or by thickening of its wall It usually contains inspissated muddy bile with considerable amount of biliary sand in addition to calculi An associated infection may result in purulent bile As cholecystitis of long standing precedes the clinical manifestations of choledocholithiasis in many cases the gall bladder meanwhile will have become atrophied and shrunken

There may be two consequences of the obstruction secondary liver damage from long standing obstruction frequently associated with infection (biliary cirrhosis) or subacute and chronic pancreatitis The mechanism of production of the latter is variable A small gallstone impacted in the duodenal orifice of the ampulla of Vater may be too large to pass into the duodenum but too small to fill completely the diverticulum and thus close the opening of the pancreatic duct As a result the bile and pancreatic ducts are converted into a continuous channel and the contents of the former reflux into the duct of Wirsung By its action on the tissues of the pancreas bile may set up a chronic inflammation Or a gallstone in the ampulla may occlude not only the bile passages but also the chief excretory duct of the pancreas blocking its secretion An infection of the secretions and of the parenchyma of the gland is then apt to occur In addition gallstones may so dilate the ampulla of Vater that intestinal contents pass into the pancreatic duct and give rise to inflammation and necrosis of the pancreas Although many other conditions associated with obstruction of the common

bile duct may give rise to chronic pancreatitis such as tumor and/or stenosis of the ampulla or impacted pancreatic calculi cholelithiasis is one of its most common causes

Choledocholithiasis is more common in women than men since cholecystic disease is also more common in women

Stones in the ductus choledochus are encountered at both extremes of age but are most common in middle life In the young *the presence of biliary calculi should* always arouse one to suspect a blood dyscrasia It is most important to recognize this disorder, *for the surgical removal of stones in these patients will* invariably be followed by recurrence as long as the underlying disease exists

Pain jaundice chills and fever are the classical symptoms of a common duct stone Still in a certain and small percentage of cases *any one or all of these symptoms may be absent* Calculi in the common duct do not always produce obstruction and consequently *their presence is not always characterized clinically by jaundice In* certain instances there may be no history of jaundice at any time *as when the stone or stones are too small or the duct widely dilated* as a compensatory process

On the other hand either in the presence or absence of icterus there may be no pain Although painless obstructive jaundice is *more commonly due to carcinoma of the duct or pancreas* such exceptions to the rule must be kept in mind In the absence of pain *the patient with calculous obstruction* and biliary cirrhosis may well be mistaken for a case of parenchymatous jaundice and denied operation on the assumption that the entire symptom complex is the result of portal cirrhosis when actually the trouble is that there is a stone in the ductus choledochus and hepatitis is secondary to the stone It is true that the latter condition is more likely to be found in a patient who gives a history of biliary colic or intermittent attacks of fever Nevertheless it is worth remembering that there is a possibility of choledocholithiasis in a jaundiced patient even though the history of the characteristic biliary colic is lacking In many such cases the stones can be demonstrated only if the patient is given the benefit of abdominal exploration

Rarely there is no history of either jaundice or pain but only recurrent febrile attacks that are associated with nausea and vomiting Still more rarely there are instances of so-called silent common duct stone with no history of pain jaundice chills or fever *Chole-*

TABLE XXXI

COMMON DUCT STONE
Clinical Features—The disease is most common in middle age and among females. In many patients there is a history of many years of intermittent flatulent indigestion and upper abdominal discomfort punctuated by attacks of biliary colic. Pain, jaundice, chills, and fever are the classical symptoms. A colicky type of pain is the most common. It is localized to the epigastrium with radiation to the back (right subscapular or interscapular region). Jaundice characteristically fluctuates. Chills and fever comprising the intermittent hepatic fever of Charcot may be present. Tenderness and rigidity in the upper right quadrant of the abdomen are present during the attack of biliary colic. The stools are intermittently clay-colored.
Laboratory Findings—The van den Bergh reaction is positive direct and bilirubinemia fluctuates rapidly within a wide range. Opaque calculi may be seen in some patients on survey films of the abdomen. Cholecystographic study may yield disappointing results.
Differential Diagnosis—The condition is to be differentiated from acute hepatitis and malignant biliary obstruction. Malignancy is more likely to occur in males. In the case of neoplasm the history is of shorter duration, the colic is less prominent, and icterus, instead of fluctuating within a wide range, continues to mount and is unremittent while the evidence of biliary obstruction persists, the obstruction finally becoming complete. In most patients with a common duct stone there is no emaciation and the course is not progressively downhill except in long-neglected cases. The long-standing history of cholelithiasis helps to differentiate the condition from acute hepatitis.

docholithiasis may then be an incidental and quite unexpected finding on autopsy.

In a typical case there can be elicited a past history of cholecystitis and cholelithiasis with chronic and persistent indigestion and specific intolerance to certain types of food. Reflex gastric and duodenal disturbances may suggest a peptic ulcer. At times an anginal-like syndrome is encountered. Choledocholithiasis produces an exacerbation of previous indigestion, flatulence, and dull upper abdominal pain with or without radiation to the back and interscapular region.

A colicky type of pain is the most common, but the pain may be less severe and dull in character or assume the form of mere

abdominal distress It may be localized to the right upper quadrant of the abdomen or radiate to the left upper quadrant and back Residual pancreatitis may lead to recurring attacks of abdominal pain like those of biliary colic Nausea and vomiting are frequent as in all other conditions of distention of a hollow viscus There may be diarrhea from lack of bile and pancreatic secretions in case of obstruction of the pancreatic duct

Icterus usually follows an attack of biliary colic *In some patients* the latter may bear no relation to the onset of jaundice which may be present before the onset of pain The colic may not be the out standing symptom the principal finding being a long standing variable jaundice simulating either parenchymal liver disease or neoplasm

Jaundice is not constant and is characterized by intermittency Biliary obstruction may be complete at times but hardly ever re mains complete for more than a few days at a time For this reason the stools and duodenal contents always contain some bile and icterus usually is variable and only slight or moderate in intensity This is in contrast to complete and permanent obstruction from stricture or malignancy

In some patients jaundice is hardly noticeable in others it is fairly well pronounced and may even become quite marked In the *absence of complicating lesions in the liver and pancreas* the bili rubin concentration in the serum averages 5 mg per cent There may be rapid fluctuations in serum bilirubin related to inconstancy of obstruction Such rapid variations are rarely seen in any other type of jaundice and therefore assume a diagnostic significance When icterus is continuous and intense without much fluctuation some cause other than biliary calculi is usually responsible The *floating gallstones* produce a ball valve effect and this explains the usual intermittent character of pain and biliary obstruction along with variations in the depth of jaundice Increase in the intensity of icterus and its greater constancy may be secondary to associated pan creatitis and/or cholangitis or secondary liver damage (biliary cir rhosis) In general cholangitis and pancreatitis and more frequently hepatitis are the usual accompaniments of both calculous and non calculous cholecystic disease

The ball valve action of the stone in an inflamed and infected *ductus choledochus* gives rise to intermittent Charcot fever with

Generally speaking a diagnosis of a common duct stone may be made when there is a history of long standing dyspepsia suggestive of cholecystic disease finally culminating in an acute attack of ague like seizures of biliary colic accompanied by jaundice chills and fever and when there is in addition evidence of *intermittent* biliary obstruction with definite variations in the *intensity* of icterus

In a patient with biliary colic and jaundice who has previously been operated upon for gall bladder trouble choledocholithiasis *must be seriously considered in the differential* diagnosis

Stricture of the Bile Ducts

The causes of benign stricture of the bile ducts may be listed as follows (modified after Cattell)

1 Ulceration from gallstones
2 Inflammation of main bile *duct*
3 Operative injuries
   (a) Excision of duct portion
   (b) Clamping during operative hemorrhage
   (c) Following subtotal gastrectomy
4 Congenital

Ulceration from gallstones is a rare complication Calculi may become impacted at the junction of the cystic and main ducts and ulcerate destroying the anterior wall of the ductus choledochus As the ulcerated areas heal sufficient constriction to produce actual stricture may result

Complete obliteration of the bile ducts resulting from a diffuse inflammatory process (cholangitis) is also rare Cholangitis tends to be recurrent and the end result may be a fibrous duct with a greatly diminished lumen or an altogether obliterated fibrous cord

Operative injuries constitute by far the most common cause of benign stricture Such injuries occur as a result of clamping the common duct in an endeavor to control the hemorrhage from an accidentally torn cystic or right hepatic artery Or the common duct may be partially obstructed by placing the cystic duct clamp too closely on the wall of the ductus choledochus A portion of the latter may also be erroneously excised during the cholecystectomy

procedure This unfortunate thing may also happen during a sub total gastric resection for duodenal ulcer when the latter is en countered on the posterior wall of the duodenum coming into close relation to the lower end of the common duct In general surgical trauma may easily occur because of frequent anatomic variations in the extrahepatic biliary channels or adhesions between the cystic and common ducts

The majority of strictures are localized and annular The fibrous stricture usually possesses some narrow channel and therefore the obstructive jaundice is not total

Stricture of the common duct should be suspected in a patient in whom jaundice appears within a comparatively short time fol lowing a previous cholecystectomy particularly when there is a his tory of hemorrhage from the cystic or right hepatic artery during the operation or when there is an associated persistent biliary fistula

While in most cases the icterus develops within a relatively short period of time (a couple of months) after the original operation in some instances it may be a late occurrence (months or years) supposedly because of the development of an obliterative cholangi tis This happens because the damaged duct is of sufficient caliber to permit the passage of bile Secondary infection in the biliary tract however produces inflammatory changes that narrow still further the lumen of the duct

The symptoms and signs will depend upon the duration and completeness of biliary occlusion and the degree of secondary hepatic injury that occurs in any case of long standing obstruction The jaundice may be painless or painful but only rarely does the pain assume the proportions of a true biliary colic Dull aching abdominal distress followed by chills and fever is not uncommon The patient frequently complains of severe and persistent pruritis Because of the combination of biliary obstruction and infection biliary cir rhosis with or without splenomegaly may develop in neglected cases Finally emaciation anemia hemorrhagic tendencies and the ter minal picture of hepatic coma supervene The jaundice is fairly constant the value for serum bilirubin averaging 10 mg per cent in the majority of instances In cases of long standing the liver function tests indicate definite impairment (hippuric acid synthesis)

Carcinoma of the Common Bile Duct

Primary cancer of the extrahepatic biliary passages is rather rare However it is more frequent than primary carcinoma of the gall bladder While malignancy of the hepatic ducts with or without involvement of the cystic duct and gall bladder remains for the most part an inoperable lesion neoplastic obstruction of the com mon duct is frequently not only operable but curable Carcinoma appears to have a predilection for the lower end of the ductus choledochus It may be difficult to differentiate on clinical grounds between the growth at the terminal portion of the common bile duct or in the ampulla of Vater and that involving the extrahepatic biliary channels more proximally located But inasmuch as a fair degree of operability has been established in malignant lesions of the terminal portion of the ductus choledochus and in periampul lary neoplastic disease it is imperative to make as early a diagnosis as possible so as to give the patient the benefit of exploration with out undue delay In a collected review of 124 cases of carcinoma of the ampulla of Vater and periampullary carcinoma in which radical extirpation of the lesion had been carried out there was a gross operative mortality of 30 6 per cent

In contrast to carcinoma of the gall bladder males are affected somewhat more often than females (57 per cent in Rolleston s series 62 per cent in the Mayo Clinic series and 65 per cent in Devic and Gallavardin s series) The lesion has been found in per sons ranging in age from 35 to 81 but is more common past 50

Biliary calculi were an associated finding in more than 50 per cent of cases reported by Marshall The stones are found less fre quently than in cases with malignancy of the gall bladder (25 to 30 per cent as compared with 75 per cent) The etiological relation between the two i e the question of priority in the occurrence of calculi and malignant growth is not clear Prior to the develop ment of obstructive jaundice the condition may easily be mistaken for gall bladder or gallstone disease but actually there is only rarely a marked degree of pain present Jaundice is the main symptom and complete biliary obstruction is present clinically in over 90 per cent of the cases

If not an initial symptom icterus occurs shortly afterwards The

most common sequence of complaints is malaise loss of strength loss of weight of energy and of appetite Irrespective of the mode of onset the principal symptoms and signs are jaundice loss of weight and strength pain pruritus anorexia nausea vomiting diarrhea or constipation alternating with chills fever a sense of weight in the abdomen flatulence and belching Nausea and vomiting are less frequent than in cases of cholecystitis and stone At the onset the condition may suggest catarrhal jaundice Pain may be present in some patients and at times may simulate a common duct stone colic In a few cases attacks of typical gallstone colic may precede by days or weeks the appearance of jaundice and paroxysmal attacks of pain associated with gallstones may occur throughout the course Some of these patients are operated on because of the erroneous diagnosis of cholelithiasis or choledocholithiasis Painless jaundice is the characteristic distinguishing feature in both carcinoma of the bile ducts and pancreas but is not universal

The liver may be normal in size or enlarged and ascites may occasionally be observed A smooth gall bladder may be palpable and of great diagnostic aid indicating malignant obstruction of the common duct although it does not differentiate the condition from that of malignant obstruction from extrinsic causes such as carcinoma of the pancreas Anemia is common The stools are clay colored once the obstructive stage is reached and usually remain so blood may be detected in the stools as a result of ulceration with bleeding from the neoplastic growth

The entire duration of the condition varies usually lasting anywhere from a few months to a year and a half Delirium and coma may be terminal events

Although in the course of observation the diagnosis of malignant obstruction can be made it is difficult if not impossible to localize the level of occlusion and to differentiate between obstruction in the common duct itself and that secondary to carcinoma of the pancreas

Carcinoma of the Papilla of Vater This is not an easy diagnosis to make although on the other hand it is not difficult to suspect or postulate definitely that one is dealing with obstruction of the common bile duct whether it be malignant or benign The correct preoperative diagnosis is rarely made although the clinician is aware that he is dealing with obstruction of the ductus choledochus This can be seen from the table below

TABLE XXXII

VARIOUS PREOPERATIVE DIAGNOSES AND THEIR INCIDENCE IN 40 CASES OF CARCINOMA OF THE PAPILLA OF VATER

(*In 7 cases 2 diagnoses were made*)

Diagnosis	*Incidence*
Carcinoma of pancreas	15
Stone in common duct	9
Obstruction of common duct	9
Stricture of common duct	4
Cholecystitis	2
Cirrhosis of the liver	1
Hepatogenous jaundice	1
Intra abdominal malignant disease	1
Carcinoma of ampulla	1
Empyema of gall bladder	1
Carcinoma of ovary	1
Duodenal ulcer	1
Carcinoma of liver	1

After Sharpe and Comfor

The outstanding symptoms early in the course of the disease are anorexia and gradual loss of weight Loss of both strength and weight is a consistent feature Jaundice is also a constant finding frequently constituting the chief complaint In most instances it is always present, although fluctuating A mildly variable, slowly progressing icterus is most frequently encountered although it may be intermittent in some instances Intermittency may be ex plained by temporary relief of obstruction through ulceration of the neoplasm Jaundice is said to be much less intense than in carcinoma of the pancreas

Contrary to earlier opinions carcinoma of the papilla of Vater is certainly not always painless When present, the pain may be mild and continuous or colicky in nature, simulating a gallstone colic either in the presence or absence of associated biliary lithiasis Nausea and vomiting although absent initially, eventually make their appearance and may accompany severe attacks of pain, and in the presence of jaundice not infrequently lead to the diagnosis of a common duct stone Pruritis may be troublesome

The patient occasionally states that he has been passing tarry stools, indicating bleeding from the surface of the tumor Diarrhea

is not uncommon There may be chills and fever both in patients with and without common duct stone Chills and fever in association with biliary colic and intermittent jaundice present a situation again indistinguishable from a stone in the common duct In many instances both the stone and carcinoma are found at operation Generally speaking the picture may be characterized by constant fluctuating or nonfluctuating jaundice with or without chills and fever with or without pain or nonfluctuating or fluctuating jaundice alone

Tenderness on palpation in the right upper quadrant is frequently found A palpable smooth gall bladder when present is the most important finding as it focuses one s attention on the prospects of malignant obstruction of the ductus choledochus whether by intrinsic growth or extrinsic pressure by growth in the pancreas Further differential diagnosis may be impossible Probably in all cases or nearly so the gall bladders are enlarged but not all are clinically palpable

There is bilirubinemia with a positive direct van den Bergh reaction In one series of cases the concentration of bilirubin ranged from 1 0 mg to 28 8 mg and averaged 14 6 mg per 100 cc of serum The urine contains bile stools are clay colored and may show blood The tendency for ampullary lesions to bleed is very definite Small amounts of bile may sometimes be obtained by duodenal intubation and blood is frequently found in the duodenal contents Occasionally the stools are steatorrheal owing to involvement of the pancreatic duct Anemia is frequent The determination of enzymes in the serum often reveals increased activity (elevation of serum lipase) but does not help in differentiating among various types of pancreatic disease Like the finding of a smooth palpable gall bladder this information points to both possibilities i e that either the pancreas or the papilla of Vater is the site of the lesion

The secondary involvement of the liver (hydrohepatosis) which results from all types of malignant obstruction may become very marked and if unchecked will produce irreversible hepatic injury The condition may be tolerated for a time by certain patients but in other cases the disintegration of the liver progresses at a more rapid pace Thus hepatic insufficiency with hemorrhagic diathesis may supervene

When the common duct is not completely obstructed by growth

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When the common duct is not completely obstructed by growth

the condition must be differentiated from hepatocellular jaundice In the presence of fluctuating icterus associated with pain the malignancy must also be distinguished from a common duct stone Such differentiation may be difficult in the absence of a palpable gall bladder and the malignant nature of the lesion may be only suspected from the progressively downhill course of the disease and the presence of gross or occult blood in the stools In the presence of consistently complete obstruction and particularly when associated with a distended gall bladder and gastro intestinal bleeding the diagnosis of malignancy is relatively easy although it may be impossible to localize on purely clinical grounds the growth in the bile duct or the pancreas Usually the two conditions are indistinguishable clinically (See Fig 18)

Carcinoma of the Gall Bladder

Carcinoma of the gall bladder affects women more frequently than men in a ratio of 4 or 5 to 1 The reason for this is that women are more apt to develop gallstones while cholelithiasis is found in the carcinomatous gall bladders with a striking frequency (60 to 90 per cent of the cases) The comparative incidence of gall bladder carcinoma in male and female patients is in practically the same ratio as that of cholelithiasis It appears that the presence of gallstones in such a high percentage of carcinomatous gall bladders may be in the nature of cause and effect relationship It was held by Ewing that mechanical irritation of calculi the relation to a peculiar form of lipoid metabolism (cholesterol) and the irritative and digestive action of bile seem to combine in producing the remarkable susceptibility of the mucous membrane to cancer An unknown carcinogenic factor in addition to a mechanical factor is probably also present

Jaundice may result from the mechanical obstruction of the common bile duct through the extension of the primary growth or by associated biliary calculi in the common duct In other cases the icterus may be secondary to massive metastases to the liver

Because of the presence of gallstones in the majority of patients with carcinoma of the gall bladder there is often a previous history of cholecystitis or cholelithiasis. Nausea belching anorexia indigestion and constipation are frequent complaints The cardinal



Fig 17 Xanthomatous nodules along the tendon sheath Xanthomatous biliary cirrhosis From F W Hoffbauer G T Evans and C J Watson Courtesy of *M Clin of N America*





Fig 18 A roughly circular deformity of the mucosal pattern of the duodenum in the region of the ampulla of Vater was the only roentgenologic evidence of a small carcinoma of the ampulla From F D Kiefer and M Moravec Courtesy of *Surg Clin N America*

Fig 19 The typical signs of pressure on the duodenum by a mass in the head of the pancreas are evident The mucosal folds are widely separated and flattened From F D Kiefer and M Moravec Courtesy of *Surg Clin N America*

symptoms are pain in the right upper quadrant and epigastrium, loss of weight, and jaundice Icterus is present, however, in only about half the cases, and when present is constant Stools then are acholic, and though chills and fever are not very common, they do occur. The pain is frequently dull and persistent, being localized to the epigastrium or to the right upper quadrant of the abdomen Such persistence of pain is uncommon in inflammatory disease of the gall bladder or malignancy of the common bile duct and pancreas

The roentgenogram may be of assistance before cystic duct occlusion occurs However as most carcinomas arise near the neck of the gall bladder, the organ is obstructed and damaged and quite frequently cannot be visualized Nonvisualization of the gall bladder by the dye method, poor concentration and slow emptying and filling defects particularly when close to the wall at least suggest that one may be dealing with a papillomatous growth

The diagnostic sign, when present is that of a palpable gall bladder, hard, irregular, and tender, which may be firmly fixed and immovable The tenderness, irregularity, and hardness of the mass distinguish it from the smooth non tender somewhat movable gall bladder distended by back pressure form malignant obstruction of the common bile duct The liver may be enlarged The presence of a hard, nodular, painful tumor in the region of the gall bladder may well be the basis for a presumptive diagnosis of carcinoma of the gall bladder, when the tumor is associated with a history suggestive of a chronic cholecystitis or cholelithiasis, loss of weight and anemia, particularly in a person over 50

Carcinoma of the Pancreas

Cancer of the pancreas is the most common of the malignant lesions causing obstructive jaundice The diagnosis offers one of the most challenging problems in the field of internal medicine Until comparatively recently the cure of malignant disease of the pancreas was considered hopeless, and the diagnosis was important only for establishing prognosis and ruling out other obstructive conditions such as common duct stone, which are curable However, since more recent advances in surgery have brought surgical cure of at least some cases of carcinoma of the pancreas within the range of possi

bility, the diagnosis assumes additional practical significance from the standpoint of therapy

The classical picture is that of painless progressive jaundice with dilatation of the gall bladder the syndrome of pancreatico bilaire of Bard and Pic later emphasized by Courvoisier However more often than not there exist some variations in this picture Frequently

TABLE XXXIII

INCIDENCE OF JAUNDICE IN CANCER OF THE HEAD AND THE BODY OR TAIL OF THE PANCREAS

	Location of the Tumor				
	Head of Pancreas		*Body and/or Tail of Pancreas*		*Total*
	Duff	*Kaplan & Angrist*	*Duff*	*Kaplan & Angrist*	
Number of cases with jaundice	13	13	8	6	40
Number of cases with out jaundice	3	12	8	8	31
Total	41		30		71

there is pain occasionally jaundice is intermittent and sometimes there is no jaundice at all By contrast with cancer of the head of the pancreas the involvement of the body and tail of the organ have been considered to be associated with icterus but very rarely, the syndrome pancreatico solaire of Chauffard Yet cases have been encountered in which jaundice is present It is not necessarily a much later manifestation in the cases originating in the body and/or tail

In the presence of jaundice the correct diagnosis can be made more readily and in its absence it is practically impossible until at least much later stages of the disease for the primary tumor, whatever be its location does not of itself produce distinctive symp-

toms The growth is deeply placed and is not amenable to detection by means of an ordinary examination In nonjaundiced patients no symptom sign laboratory test, or roentgenologic finding is pathognomonic of carcinoma of the pancreas It is only when the

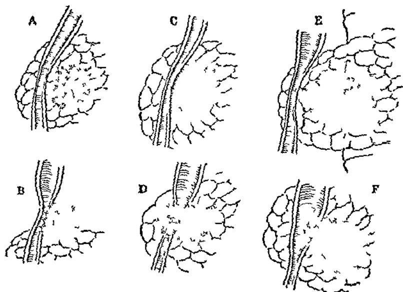
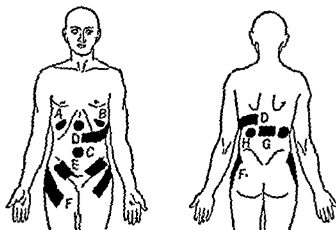


Fig 20 Diagrammatic representations of mechanisms of obstruction of duct by cancer (a) Tumor mass in head of pancreas displacing but not obstructing lumen of duct (b) Tumor mass just above pancreas possibly lymph node extending to wall with local annular stenosing scirrhous reaction causing obstruction of relentless progressive character (c) Tumor in head of pancreas extending to wall of duct fixing and displacing same with some narrowing of lumen It is obvious that progressive growth of tumor as a whole leads to further direct impingement upon lumen (d) Tumor of head of pancreas with extension to duct wall and mechanism of annular stenosis and tumor extension both operative in producing obstruction (e) Tumor of pancreas that is fixed to vertebral bodies and that also displaces the duct with kinking and narrowing of lumen (f) Tumor of head of pancreas without scirrhous reaction with medullary tumor extension into lumen often associated with intermittent jaundice brought on by repeated sloughing of intraluminary tumor extension From N Kaplan and A Angrist
Courtesy of *Surg Gynec and Obst*

biliary tract becomes secondarily affected that recognizable symptomatology makes its appearance In the absence of such involvement of the biliary system only the spread of the tumor by extension to the adjacent organs or distant metastases lead to its detection

It is taken for granted that jaundice in cancer of the head of the pancreas is due to extrinsic (extraductal) compression of the ductus

choledochus and in the cases of cancer of the body and/or tail is likewise produced by compression of the biliary passages by metastatic lymph nodes in the region of the porta hepatis However, it has been shown that whereas a growing mass in a fixed organ like the pancreas might cause compression of the ducts enlarging lymph nodes at the porta hepatis have room for expansion and should not cause blocking unless they are fixed to the duct wall, to the sur



... f the pancreas ... al ... om

rounding structures or to both Such fixation of the bile duct structures by the tumor are the necessary mechanism of the production of obstruction and jaundice First invasion fixes the wall of the duct and permits of physical compression with narrowing of the lumen instead of mere displacement by the adjacent expanding tumor mass Second the invasion of the duct wall is accompanied by a scirrhous reaction and production of an annular stenosing lesion with localized segmental narrowing and obstruction of the lumen Finally the invasion of the duct wall may be associated with extension to and filling of the lumen by tumor tissue with obstruction of the flow of bile

The disease generally occurs in persons over forty The onset may be gradual and painless the more definite symptoms being preceded by general failure in health Marked loss of weight anorexia and progressively increasing weakness are the most constant findings

Weight loss sometimes totaling as much as 40 or 50 pounds is almost invariably evident Pain and jaundice may or may not be present The pain frequently extends across the upper part of the abdomen to the left side and may even be felt in the left supra scapular region It may precede or follow icterus The biliary obstruction when present is characterized by completeness and per manence Once jaundice supervenes it is progressive and becomes deep and constant The reader will recall that the maximal degrees of bilirubinemia are seen in neoplastic obstruction and in the more severe forms of hepatocellular jaundice The icterus assumes a greenish tinge

Among the less common symptoms are hematemesis or melena

TABLE XXXIV

MALIGNANT BILIARY OBSTRUCTION
(*Carcinoma of the Pancreas or Ampulla of Vater*)

Clinical Features—The greatest number of cases occur in persons in the sixth decade of life It is a rapidly progressive disease Although a persistent painless jaundice constitutes a classical description of the disease abdominal pain is encountered in about 50 per cent of the cases Loss of weight fatigue weakness and anorexia may be prominent Enlargement of the gall bladder *in the* presence of complete biliary obstruction is practically pathognomonic of the disease The liver eventually becomes enlarged (biliary cirrhosis) Splenomegaly and ascites may supervene Once *the* stools become clay-colored they remain so indefinitely

Laboratory Findings—Anemia is common The van den Bergh reaction is positive direct Bilirubinemia mounts stead ly The bile pigments gradually disappear entirely from the stools, indicating a complete and constant biliary obstruction The disappearance of urobilin from the urine points in the same direction The presence of blood in the stools is significant Early in the disease the liver function tests indicate lack of hepatic impairment but with the advent of the disease the liver function suffers as biliary cirrhosis develops secondary to long standing obstruction X ray findings may be helpful *in* demonstrating the tumor by indirect evidence (pressure defects in gastro-intestinal studies)

Differential Diagnosis—The first step consists in demonstrating that jaundice is of an obstructive nature Permanency of obstruction *in the* presence of a palpable gall bladder practically establishes the diagnosis of malignant occlusion of the common bile duct. Evidence of gastro-intestinal bleeding also aids *in* the diagnosis

Gastro intestinal bleeding occurs for one of the following reasons the tumor may have eroded into the stomach or duodenum, *oesophageal* varices may have formed secondary to neoplastic invasion and thrombosis of the splenic or portal vein, obstructive jaundice may have led to hypoprothrombinemia

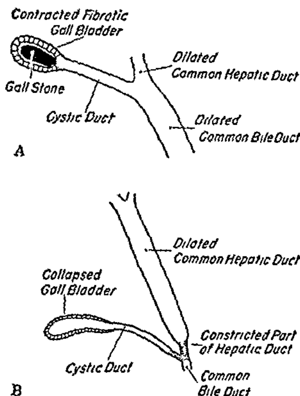


FIG 22 Schematic representation of the conditions in which the gall bladder fails to enlarge in the *presence of complete obstruction of the common duct by neoplasm* (a) Calculous cholecystitis found in association with carcinoma of the head of the pancreas. (b) Congenital anomaly of the extrahepatic biliary system

The liver is frequently palpable, firm and usually with a rounded edge, and in some instances there may be ascites The spleen is felt occasionally In the presence of jaundice the characteristic finding is a palpable, non tender, smooth gall bladder, which is found however, in somewhat less than half of the icteric cases The traditional picture of painless jaundice and a palpable distended gall bladder is observed in only 25 to 40 per cent of all patients with carcinoma of the pancreas, and in such instances is followed by distention of the

whole duct system The tumor may occlude the pancreatic duct, under these circumstances fatty diarrhea may develop for obvious reasons Commonly there is no fever and the tempearture may even be subnormal

Anemia is frequent bilirubinemia may be very marked and the van den Bergh reaction is direct positive The characteristic laboratory findings in jaundiced patients demonstrate complete and constant biliary obstruction Stools are acholic and no urobilin can be recovered from the feces or urine for indefinite periods Even repeated duodenal intubation reveals no trace of bile However the obstruction is not always complete and small amounts of bile may be recovered Bloody mucous plugs and even gross hemorrhage may be detected by duodenal drainage or examination of the stools The blood comes from the necrotic surface of the growth or for other reasons mentioned above and when recovered in the stool or duodenal contents is of great help in determining the presence of neoplastic obstruction The feces usually have an acid reaction and may contain a high percentage of unabsorbed fat Creatorrhea may be found in addition to steatorrhea

The concentration of cholesterol in the plasma is moderately increased and an elevated value for serum phosphatase may be found At the onset the liver function tests, such as galactose tolerance and hippuric acid excretion are negative thus serving to distinguish the condition from hepatogenous jaundice in which the evidence of functional liver impairment is obtained early However after biliary obstruction has been present for several weeks the results of these tests may be reversed as secondary liver damage is produced making the character of jaundice less clear-cut

In some patients abnormalities in carbohydrate metabolism occur This observation has been made more frequently than can be accounted for on the basis of chance An elevated curve with the glucose tolerance test may be explained either on the basis of neoplastic replacement of the islands of Langerhans or pre existing diabetic state In many instances the diabetes antedates the symptoms of pancreatic malignancy by many years This suggests the possibility that diabetes is occasionally the precursor of cancer of the pancreas

There are certain roentgenological findings that may be of some help by demonstrating deformities and displacements of the stom

ach, duodenum, or colon, indicating the presence of a tumor in the region of the pancreas The antrum of the stomach may be seen to be fixed and deformed This sign, however, is not conclusive, because an infiltrating gastric neoplasm on the posterior wall may have a similar appearance The most characteristic finding is a widened sweep of the duodenum that normally curves around the pancreatic head, and the production of the inverted 3 figure (See Fig 19 p 242) The mucosal folds can become widely separated and flattened An ingenious method of visualizing the pancreas consists of having the patient lie prone, inflating the stomach with air through a tube or giving an effervescent mixture, and then taking a lateral roentgenogram The gas in the stomach outlines the dorsal aspect of this organ, and the pancreas appears as a shadow between the air filled stomach and the lumbar spine Broadening of this shadow indicates enlargement of the pancreas False positive results may occur in short, thick set individuals who have excess retroperitoneal fat

After jaundice is established as obstructive, several forms of common duct occlusion must be ruled out before a diagnosis of carcinoma of the pancreas can be made In the presence of obstructive jaundice, a distended, palpable gall bladder and evidence of gastrointestinal bleeding are indicative of the malignant nature of the offending lesion Although not a constant finding, they are the most reliable signs However, there is no way of differentiating carcinoma of the pancreas from carcinoma of the common bile duct or the ampulla of Vater The roentgenological findings above referred to may be of some limited value in localizing the site of obstruction when roentgenological evidence of a pancreatic tumor is present A painless common duct stone is also difficult to differentiate In this condition, jaundice is usually fluctuating and intermittent

Very rarely chronic pancreatitis may produce biliary obstruction and result in a clinical picture similar to that of obstructive jaundice secondary to carcinoma The two conditions can be distinguished only with great difficulty clinically and even on laparotomy as chronic pancreatitis may result in a hard mass in the pancreas characteristic of malignant growth, and the surgeon may remain under the impression that he is palpating a carcinoma Of course, the subsequent course will prove the condition to be benign

Conclusions

It must be admitted that in certain instances it is practically impossible to make an accurate differential diagnosis between an obstructive and nonobstructive type of jaundice There are patients encountered in whom on careful study the weight of evidence is in favor of a nonobstructive or hepatocellular disease Still, the clinician is unable to exclude definitely the question of an obstructive lesion It is felt by some that the problem may be solved by observation of these patients for a certain period of time say six weeks, particularly if there is a trend toward diminution in the intensity of jaundice In the latter case icterus may be assumed to be of hepatic origin, and in many instances this does no harm Such a consideration, however, is complicated by cases of hepatogenous jaundice that last longer than the period specified above Moreover, one should attempt to avoid certain effects of prolonged jaundice in patients in whom it may be due to an obstructive lesion, particularly when the latter is amenable to successful surgical treatment Early surgical exploration is in order when there is any justifiable suspicion of an obstructive lesion In other words, in highly questionable cases in which extrahepatic obstruction cannot be excluded, surgical exploration should receive due consideration Even once the obstructive nature of jaundice is rather definitely established on purely clinical grounds, the question of the malignant versus benign character of the underlying process may present the next difficulty Can the patient benefit by the operation? Can a cure be effected? It would be appropriate to close this discussion with the following quotation from Sir Berkeley Moynihan

No one living is infallible in the differential diagnosis of obstructive jaundice The diagnosis is always so difficult, and the chance of a life saved so important, that, however positive the evidence of malignancy may be, I now advise operation in all cases . It is impossible for the most astute clinician or the most subtle pathologist to discover by physical signs from the anamnesis or from the chemical examination of urine and feces, whether a simple or a cancerous disease is present He may shrewdly guess, but a guess is a poor peg on which to hang a man's life. All cases of obstructive jaundice should be treated by operation.

BIBLIOGRAPHY

Bard L and Pic A *Rev Med* 8 257 1888
Barron M *Arch Int Med* 35 807 1925
Berk J E *Arch Int Med* 40 1 19 7 ibid 68 523 1941
Cattell R B *Surg Clin N Amer*, 23 701 1943
Clute H M J *J A M A* 107 91 1936
Courvoisier *Casuistisch statistische Beitrage zur Pathologie und Chirurgie der Gallenwege* Leipzig F C W Vogel 1890
Devic and Gallavardin L *Rev de med* 21 557 1901
Duff G L *Bull Johns Hopkins Hosp* 65 69 1939
Friedenwald J and Cullen T S *Am J Med Sci* 167 31 1928
Henry K P *Canad M A J* 42 251 1940
Hunt V C *Western J Surg Obst and Gynec* 50 327 1942
Hunt V C and Budd J W *Surg Gynec and Obst* 61 651 1935
Jordan F M and Weir J F *Med Clin N America* 15 1529 1932
Judd E S and Marshall J M *J A M A* 95 1061 1930
Kaplan N and Angrist A *Surg Gynec and Obstr* 77 199 1943
Kiefer E S and Moravec M *Surg Clin N America* 23 788 1943
Kirklin B R *Am J Roentgenol* 29 8 1933
Lam C R *Ann Surg* 111 403 1940
Levy H and Lichtman S S *Arch Int Med* 65 607 1940
Lichtenstein G M and Tannenbaum W *Ann Surg* 111 411 1940
Lieber M M Stewart H L and Lund H *Ann Surg* 109 219 1939
Meyer K A and Steigmann F *Surg Gyn & Obst* 67 640 1938
Moynihan Sir Berkeley *Abdominal Operations* Philadelphia W B Saunders Company v ii 1926
Oertel N *Arch Int Med* 21 73 1918
Ransom H K *Am J Surg* 40 264 1938
Rolleston H S and McNee J W *Diseases of the Liver Gallbladder and Bile Ducts* London Macmillan Company 1929
Sharpe W S and Comfort M W *Am J Med Sci* 202 238 1941
Snell A M *Canad M A J* 37 318 1937
Walters W *Surg Gynec and Obst* 63 417 1936
Walters W and Snell A M *Diseases of the Gallbladder and Bile Ducts* Philadelphia W B Saunders Company 1940
Watson C J *J.A.M.A* 114 2427 1940
Weir J F *Am J Surg* 5 494 1932
Weiss S *Clinical Lectures on the Gallbladder and Bile Ducts* Chicago, The Year Book Publishers 1944
Whipple A O *Trans Am Surg Ass* 45 143 1927

APPENDIX

Malignant and Fulminant Forms of Infectious Hepatitis

Reference has already been made to the fact that although acute (infectious or epidemic) hepatitis usually tends to run a benign course, terminating within a shorter or longer time in complete recovery, now and then a few cases run either an acute lethal course or terminate in cirrhosis. With widespread prevalence of epidemic hepatitis during the last war there are indications that the disease has become more severe and a more fulminant course of fatal hepatitis has been observed during the past two years.

Clinically, this fulminant form of hepatitis is characterized by the short and stormy course of less than ten days duration, the frequency of high fever during the prodromal stage, and the brevity of the icteric stage. Deaths on as early as the second, third, fourth, and fifth days of the disease are not uncommon, with most fatalities occurring on the ninth day. The onset is ushered in by one of two syndromes: (1) an infectious type with high fever, chilliness, malaise, and general aching dominating the picture, and (2) a gastrointestinal type with anorexia, nausea, and epigastric discomfort in the foreground. Sometimes initial symptoms of both types appear simultaneously. The prodromal symptoms do not differ significantly in type or severity from those of the usual non-fatal cases. The temperature ranges from 95° to 104° and averages 102° F., fever declining as a rule with the onset of jaundice. During the final stage of the disease there is usually a sharp rise in temperature coincident with profound cerebral disturbances. Jaundice is often mild and several anicteric cases have been reported. In some instances jaundice occurs at the onset of symptoms, while in others it is delayed until the day of death. On an average it appears on the second or third day after the beginning of symptoms. Early jaundice tends to

occur in the more fulminant cases It may deepen rapidly during the final phase which is marked by abrupt change for the worse and is characterized by cerebral symptoms and signs such as listlessness drowsiness increasing apathy or restlessness excitement and even maniacal state hyperactive reflexes positive Babinski sign and ankle clonus Vomiting is frequent and severe and hemorrhagic tendencies with frank gastro intestinal bleeding and purpuric phenomena are not uncommon The pulse is usually rapid and bradycardia is seen but rarely Hepatic pain may be severe The liver is moderately enlarged and usually tender during the late prodromal and early icteric stages As the disease progresses the liver may shrink but not invariably so The spleen becomes palpable in about 25 per cent of the cases Ascites may occur Urinalysis reveals the presence of albumin bile and casts Leucine and tyrosine crystals are conspicuous by their absence The fall in blood sugar and the low value of blood urea nitrogen reflect rapid and massive necrosis of the hepatic parenchyma However these laboratory findings are not constantly present

Pathologically the outstanding lesions are extensive and comprise uniform destruction of liver cells minimal evidence of regeneration and marked inflammatory reaction with inflammatory infiltration especially of the portal areas and the perilobular boundaries In contrast with the cases running a subacute course there is no noteworthy degree of regenerative hyperplasia Regeneration obviously cannot take place when destruction of the parenchyma is complete Although the term acute yellow atrophy implies a rapid breakdown of the hepatic parenchyma it is not descriptive of the appearance in the group of cases under discussion In the more rapidly fatal cases the lesions are older than the clinical manifestations In other words when symptoms first appear the liver must already be definitely involved Thus in some instances the clinical course may be silent or the symptoms minimal even when death occurs within a few days

The possibility may be entertained that the course described above represents a disease different from epidemic hepatitis However it has been pointed out that similarities are greater than the differences and that these differences in turn are quantitative rather than qualitative Also all grades of transition between the fulminant and benign forms of hepatitis have been noted

Another variant of infectious hepatitis recently observed is that of the disease with serious but protracted course and high fatality rate Peculiarly enough the disease is most prevalent in middle aged women The duration most commonly is from four to nine months but both much more acute and more protracted courses have been noted The clinical course is characterized by jaundice frequent febrile attacks of pain and development of symptoms of portal stasis (ascites) The liver function tests demonstrate hepatic impairment Pathologically the process is characterized by destruction of the liver tissue In the more chronic cases cicatrized connective tissue develops Clinically and perhaps also etiologically the disease seems to differ from acute infectious hepatitis Some cases of persistent and chronic jaundice with hepatitis may belong in this particular group

BIBLIOGRAPHY

Alsted G *Am J Med Sci* 213 257 1947
Horan T H Jolliffe L S and Mallory T B in press
Lucké B and Mallory T B *Am J Path* 22 867 1946

PATHOGENESIS OF JAUNDICE

In the chapter on the pathogenesis of jaundice the following factors have been mentioned as explaining the mechanism of icterus production in liver disease (1) parenchymal damage leading to disruption of the continuity of the biliary canaliculi and resulting in biliary stasis with bile thrombi (2) compression of the canals of Hering by exudate in the periportal spaces (3) pericholangitis and bile thrombi in the liver biliary radicles in the absence of parenchymal liver damage

In fulminant hepatitis destruction of liver parenchyma is often complete Such total destruction of the hepatic columns leads to destruction of delicate biliary canaliculi and obstructive factors cannot therefore be considered It remains to account for jaundice in such cases only on the basis of the rapid destruction of liver cells their absence makes it impossible to remove bilirubin from the circulating blood In other words one is confronted here with the consideration of a retention type of jaundice in the course of a pathological process (parenchymal liver disease) which is usually

thought to be associated with the regurgitant type of icterus production Perhaps in regurgitation jaundice bilirubin brought by the circulating blood to the liver for excretion is converted to the direct reacting pigment by the Kupffer cells and then passes at once back into the circulation It will be recalled that of the three functioning units of the liver—hepatocellular biliary and reticulo-endothelial—the latter remains relatively intact whereas the other two may be completely destroyed or disorganized Kupffer cells represent a part of the reticulo endothelial system

Added difficulties are encountered with regard to fulminant hepatitis without jaundice No explanation can be offered for the absence of icterus in the presence of complete destruction of liver Apparently no consistent anatomic basis for the development of icterus has been found to date These considerations clearly indicate the need for reinvestigation of some of the complex and obviously not as yet clearly understood mechanisms of jaundice production

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